HANDBOOK OF
Pharmaceutical Manufacturing Formulations

Liquid Products

VOLUME 3

Handbook of Pharmaceutical Manufacturing Formulations

Volume Series

Sarfaraz K. Niazi

Volume 1
Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

Volume 2
Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

Volume 3
Handbook of Pharmaceutical Manufacturing Formulations: Liquid Products

Volume 4
Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products

Volume 5
Handbook of Pharmaceutical Manufacturing Formulations: Over-the-Counter Products

Volume 6
Handbook of Pharmaceutical Manufacturing Formulations: Sterile Products

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Dedication

To August P. Lemberger

Preface to the Series

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. It is anticipated that the industry will spend about $20 billion on research and development in 2004. Because patent protection on a number of drugs is expiring, the generic drug market is becoming one of the fastest growing segments of the pharmaceutical industry with every major multinational company having a significant presence in this field.

Many stages of new drug development are inherently constrained by time, but the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations into a comprehensive and, by nature, rather voluminous presentation.

The book is divided into six volumes based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and over-the-counter (OTC) products. Although they may easily fall into one of the other five categories, OTC products are considered separately to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of the product; of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of pharmaceutical products into these six categories. Each volume includes a description of regulatory filing techniques for the formulations described. Also included are regulatory guidelines on complying with Current Good Manufacturing Practices (cGMPs) specific to the dosage form and advice is offered on how to scale-up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and reduce the time required to file by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a fixed paradigm when it comes to selecting formulations: "Not invented here" perhaps is kept in the back of the minds of many seasoned formulations scientists when they prefer certain platforms for development. It is expected that with a quick review of the formulation possibilities that are made available in this book such scientists would benefit from the experience of others. For teachers of formulation sciences this series offers a wealth of information. Whether it is selection of a preservative system or the choice of a disintegrant, the series offers many choices to study and consider.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois

Preface to the Volume

Liquid products, for the purpose of inclusion in this volume, include nonsterile drugs administered by any route in the form of solutions (monomeric and multimeric), suspensions (powder and liquid), drops, extracts, elixirs, tinctures, paints, sprays, colloidons, emulsions, aerosols, and other fluid preparations. Sterile liquid products are presented in another volume. Whereas liquid drugs do not share the compression problems of solid dosage forms, the filling problems of powder dosage forms, and the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages. The considerations of prime importance for liquid drugs include solubility of active drugs, preservation, taste masking, viscosity, flavoring, appearance, and stability (chemical, physical, and microbiological), raw materials, equipment, the compounding procedures (often the order of mixing), and finally the packaging (to allow a stable product to reach patients). Suspensions present a special situation in which even the powder for reconstitution needs to be formulated such that it can be stable after reconstitution; therefore, limited examples are included here.

Chapter 1 in Section I (Regulatory and Manufacturing Guidance) describes the practical details in complying with the current good manufacturing practice (cGMP) requirements in liquid manufacturing. This chapter does not address the specific cGMP parameters but deals with the practical aspects as may arise during a U.S. Food and Drug Administration (FDA) inspection. This includes what an FDA inspector would be looking into when auditing a liquid manufacturing facility.

Chapter 2 describes the stability testing of new drugs and dosage forms. Drawn from the most current International Conference on Harmonization (ICH) guidelines, this chapter describes in detail the protocols used for stability testing not only for new drugs but also for new dosage forms. The chapter is placed in this volume because stability studies are of greater concern in liquid dosage forms; however, keeping in mind the overall perspective of the series of this title, this chapter would apply to all dosage forms. Again, emphasis is placed on the practical aspects, and the reader is referred to official guidelines for the development of complete testing protocols. It is noteworthy that the ICH guidelines divide the world into four zones; the discussion given in this chapter mainly refers to the U.S. and European regions, and again the formulator is referred to the original guideline for full guidance. Stability studies constitute one of the most expensive phases of product development because of their essential time investment. As a result, formulators often prepare a matrix of formulations to condense the development phase, particularly where there are known issues in compatibility, drug interactions, and packaging interactions. The FDA is always very helpful in this phase of study protocols, particularly where a generic drug is involved. It is also a good idea to benchmark the product against the innovator product. However, one should understand clearly that the FDA is not bound to accept stability data even though it might match that of the innovator product. The reason for this may lie in the improvements made since the innovator product was approved. For example, if a better packaging material that imparts greater safety and shelf life is available, the FDA would like this to be used (not for the purpose of shelf life, but for the safety factors). In recent years, the FDA has placed greater emphasis on the control of Active Pharmaceutical Ingredient (API), particularly if it is sourced from a new manufacturer with a fresh DMF. Obviously, this is one way how the innovator controls the proliferation of generic equivalents. The original patents that pertain to synthesis or manufacturing of the active raw material may have been superseded by improved processes that are not likely to be a part of a later patent application (to protect the trade secret because of double-patenting issues). The innovator often goes on to revise the specifications of the active pharmaceutical ingredient to the detriment of the generic manufacturer. However, my experience tells me that such changes are not necessarily binding on the generic manufacturer, and as long as cGMP compliance in the API is demonstrated and the impurities do not exceed the reference standard (if one is available), there is no need to be concerned about this aspect. However, manufacturers are advised to seek a conference with the FDA should this be a serious concern. At times, the manufacturer changes the finished product specification as the patents expire or reformulates the product under a new patent. A good example of this practice was the reformulation of calcitriol injection by Abbott as its patent came to expiry. The new specifications include a tighter level of heavy metals, but a generic manufacturer should have no problem if the original specifications are met because the product was approvable with those specifications.

Chapter 3 describes the container closure systems; again, this discussion would apply to all dosage forms. It is noteworthy that the regulatory agencies consider containers and packaging systems, all those components that

come in contact with the product, protect the product from environment, or are instrumental in the delivery of the product as part of the product definition. Whereas the industry is much attuned to studies of the effects of the API and dosage formulation components, the study of container or closure systems is often left to the end of the study trials. This is an imprudent practice, as it might result in loss of valuable time. The packaging industry generally undergoes faster changes than do the chemical or pharmaceutical industries. New materials, better tolerances, more environmentally friendly materials, and now, with the use of mechanical devices in many dosage forms, appropriate dosing systems emerge routinely. As a rule of thumb, the closure system for a product should be the first criterion selected before development of the dosage form. Switching between a glass and a plastic bottle at a later stage can be a very expensive exercise. Because many of these considerations are drawn by marketing teams, who may change their product positioning, the formulation team must be appropriately represented in marketing decision conferences. Once a decision has been made about the presentation of a product, the product development team should prepare several alternatives, based on the ease of formulation and the cost of the finished product involved. It should be emphasized at all stages of development that packaging scale-ups require just as much work as does a formulation scale-up or changes. As a result, the FDA provides the scale-up and post-approval change (SUPAC) guidelines for packaging components. Changes in the dimensions of a bottle may expose a large surface of liquid to the gaseous phase in the bottle and thus require a new stability testing exercise. This chapter forms an important reminder to formulators on the need to give consideration to every aspect of the container closure system as part of routine development.

Chapter 4 introduces the area of preapproval inspections, a process initiated by the FDA in the wake of the grand scandals in the generic pharmaceutical industry a few years ago. The FDA guidelines now allow "profiling" of companies and list the requirements of preapproval inspections when an application has been filed. Whereas the emphasis in this chapter is on "preapproval," the advice provided here applies to all regulatory inspections. A regulatory inspection can be an arduous exercise if the company has not prepared for it continuously. Preparedness for inspection is not something that can be achieved through a last-minute crash program. This chapter goes into considerable detail on how to create a cGMP culture, how to examine the documentary needs, assignment of responsibility, preparation of validation plan, and above all, the art of presenting the data to the FDA. Also discussed are the analyses of the outcome of inspection. Advice is provided on how to respond to Form 483 issued by the FDA, and the manufacturer is warned of the consequences of failing an inspection. Insight is also provided for foreign manufacturers, for whom a different set of rules may be applied because of the physical constraints of inspection. The inspection guidelines provided apply to both the manufacturers of API as well as to the finished products.

Chapter 5 includes highlights of topics of importance in the formulation of liquid products. However, this chapter is not an all-inclusive guide to formulation. Only highlights of points of concern are presented here, and the formulator is referred to several excellent treatises available on the subject.

Section II contains formulations of liquid products and lists a wide range of products that fall under this classification, as interpreted in the volume. There are three levels at which these formulations are described. First, the Bill of Materials is accompanied by detailed manufacturing directions; second, the manufacturing directions are abbreviated because they are already described in another product of similar nature; and third, only the composition is provided as supplied by the manufacturer. With the wide range of formulations included in this volume, it should be a simple matter for an experienced formulator to convert these formulations into quantitative Bills of Materials and then to benchmark it against similar formulations to come up with a working formula. The problems incumbent in the formulation of liquid products are highlighted in Chapter 5, but these are generic problems, and the formulator should be aware of any specific situations or problems that may arise from time to time. I would like to hear from the formulators about these problems so that they could be included in future editions of this book. Again, the emphasis in this series is on a practical resolution of problems; the theoretical teachings are left to other, more comprehensive works on this topic. The key application of the data provided herein is to allow the formulator to select the ingredients that are reportedly compatible, avoiding need for long-term studies to establish compatibilities.

I am grateful to CRC Press for taking this lead in publishing what is possibility the largest such work in the field of pharmaceutical products. It has been a distinct privilege to know Mr. Stephen Zollo, senior editor at CRC Press. Stephen has done more than any editor can do to encourage an author into completing this work on a timely basis. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Amy Rodriguez, and others. Though much care has gone into correcting errors, any errors remaining are altogether mine. I shall appreciate the readers bringing these to my attention for correction in future editions of this volume (niazi@pharmsci.com).

This volume is dedicated to one of the great educators and a leader in the pharmaceutical profession, August P. Lemberger, who is truly a Wisconsin man. At the University of Wisconsin in Madison, he was an undergraduate

and graduate student. He was then a professor, and twice Dean of the School of Pharmacy (1943–44, 1946–52, 1953–69, 1980–91). During the period between 1969 and 1980, he assumed the responsibility of deanship at the University of Illinois, where I was a graduate student. In 1972, he offered me my first teaching job, as an instructor of pharmacy at the University of Illinois, while I was still in graduate school. I was one of the greatest beneficiaries of his kindness and attention. Gus has an unusual ability to put everyone at ease, respect everyone around him, and in the end, come out as a group leader. Whatever little I have accomplished in my life is mostly due to Gus. Many awards, recognitions, and salutations were offered to Gus during his celebrated career. His research contributions included stability studies, suspension, emulsion stabilization, and later in his career, the various aspects of pharmaceutical education. I wish him many years of happy retirement and shuttling back and forth between his homes in Arizona and Wisconsin. Thanks, Gus.

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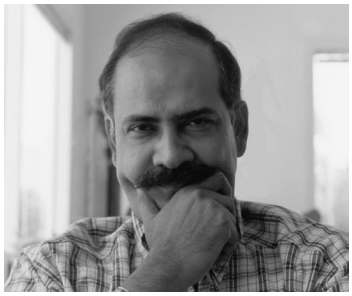

Dr. Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 30 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents and is licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from consumer products to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science of formulations and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com).

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Xylometazoline Hydrochloride Children's Nasal Solution

Part I

Regulatory and Manufacturing Guidance

1 Current Good Manufacturing Practice Considerations in Liquid Manufacturing

I. INTRODUCTION

The manufacture and control of oral solutions and oral suspensions presents some unusual problems not common to other dosage forms. Although bioequivalency concerns are minimal (except for products in which dissolution is a rate-limiting or absorption-determining step, as in phenytoin suspension), other issues have frequently led to recalls of liquid products. These include microbiological, potency, and stability problems. In addition, because the population using these oral dosage forms includes newborns, pediatrics, and geriatrics, who may not be able to take oral solid dosage forms and who may have compromised drug metabolic or other clearance function, defective dosage forms can pose a greater risk if the absorption profiles are significantly altered from the profiles used in the development of drug safety profiles.

II. FACILITIES

The designs of the facilities are largely dependent on the type of products manufactured and the potential for cross contamination and microbiological contamination. For example, the facilities used for the manufacture of over-the-counter oral products might not require the isolation that a steroid or sulfa product would require. However, the concern for contamination remains, and it is important to isolate processes that generate dust (such as those processes occurring before the addition of solvents). The HVAC (heating, ventilation, and air-conditioning) system should be validated just as required for processing of potent drugs. Should a manufacturer rely mainly on recirculation rather than filtration or fresh air intake, efficiency of air filtration must be validated by surface and air sampling. It is advisable not to take any shortcuts in the design of HVAC systems, as it is often very difficult to properly validate a system that is prone to breakdown; in such instances a fully validated protocol would need stress testing — something that may be more expensive than establishing proper HVAC systems in the first place. However, it is also unnecessary to overdo it in designing the facilities, as once the drug is present in a solution form, cross contamination to other products becomes a lesser problem. It is, nevertheless, important to protect the drug from other powder sources (such as by maintaining appropriate pressure differentials in various cubicles).

III. EQUIPMENT

Equipment should be of sanitary design. This includes sanitary pumps, valves, flow meters, and other equipment that can be easily sanitized. Ball valves, the packing in pumps, and pockets in flow meters have been identified as sources of contamination. Contamination is an extremely important consideration, particularly for those sourcing manufacturing equipment from less developed countries; manufacturers of equipment often offer two grades of equipment: sanitary equipment, and equipment not qualified as sanitary and offered at substantial savings. All manufacturers intending to ship any product subject to U.S. Food and Drug Administration (FDA) inspection must insist on certification that the equipment is of sanitary design.

To facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and standard operating procedures. Long delivery lines between manufacturing areas and filling areas can be a source of contamination. Special attention should be paid to developing standard operating procedures that clearly establish validated limits for this purpose.

Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. These products are generally formulated on a weight basis, with the batching tank on load cells so that a final volume can be made by weight; if you have not done so already, consider converting your systems to weight basis. Volumetric means, such as using a dipstick or a line on a tank, are not generally as accurate and should be avoided where possible. When volumetric means are chosen, make sure they are properly validated at different temperature conditions and other factors that might render this practice faulty. In most cases, manufacturers assay samples of the bulk solution or suspension before filling. A much greater variability is found with those batches that have been manufactured volumetrically rather than those that have been manufactured by weight. Again, the rule of thumb is to avoid any additional validation if possible.

The design of the batching tank with regard to the location of the bottom discharge valve often presents problems. Ideally, the bottom discharge valve is flush with the bottom of the tank. In some cases, valves — including undesirable ball valves — are several inches to a foot below the bottom of the tank. This is not acceptable. It is possible that in this situation the drug or preservative may not completely dissolve and may get trapped in the "dead leg" below the tank, with initial samples turning out subpotent. For the manufacture of suspensions, valves should be flush.

Transfer lines are generally hard piped and are easily cleaned and sanitized. In situations where manufacturers use flexible hoses to transfer product, it is not unusual to see these hoses lying on the floor, thus significantly increasing the potential for contamination. Such contamination can occur through operators picking up or handling hoses, and possibly even through operators placing them in transfer or batching tanks after the hoses had been lying on the floor. It is a good practice to store hoses in a way that allows them to drain, rather than coiling them, which may allow moisture to collect and be a potential source of microbial contamination.

Another common problem occurs when manifold or common connections are used, especially in water supply, premix, or raw material supply tanks. Such common connections can be a major source of contamination.

IV. RAW MATERIALS

The physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. As with topical products in which the drug is suspended, particles are usually very fine to micronized (to <25 microns). For syrup, elixir, or solution dosage forms in which there is nothing suspended, particle size and physical characteristics of raw materials are not that important. However, they can affect the rate of dissolution of such raw materials in the manufacturing process. Raw materials of a finer particle size may dissolve faster than those of a larger particle size when the product is compounded.

Examples of a few oral suspensions in which a specific and well-defined particle-size specification for the drug substance is important include phenytoin suspension, carbamazepine suspension, trimethoprim and sulfamethoxazole suspension, and hydrocortisone suspension. It is therefore a good idea to indicate particle size in the raw material specification, even though it is meant for dissolving in the processing, to better validate the manufacturing process while avoiding scale-up problems.

V. COMPOUNDING

In addition to a determination of the final volume (on weight or volume basis) as previously discussed, there are microbiological concerns, and these are well covered in other chapters in this book.

For oral suspensions there is the additional concern of uniformity, particularly because of the potential for segregation during manufacture and storage of the bulk suspension, during transfer to the filling line, and during filling. It is necessary to establish procedures and time limits for such operations to address the potential for segregation or settling as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature is important from a microbiological as well as a potency aspect. For those products in which temperature is identified as a critical part of the operation, the batch records must demonstrate compliance using control charts. There are some processes in manufacturing in which heat is used during compounding to control the microbiological levels in the product. For such products, the addition of purified water to make up to final volume, the batch, and the temperatures during processing should be properly documented.

In addition to drug substances, some additives —such as the most commonly used preservatives, parabens —are difficult to dissolve, and require heat (often to 80°C). The control and verification of their dissolution during the compounding stage should be established in the method validation. From a potency aspect, the storage of product at high temperatures may increase the level of degradants. Storage limitations (time and temperature) should be justified.

There are also some oral liquids that are sensitive to oxygen and that have been known to undergo degradation. This is particularly true of the phenothiazine class of drugs, such as perphenazine and chlorpromazine. The manufacture of such products might require the removal of oxygen, as by nitrogen purging. In addition, such products might also require storage in sealed tanks, rather than in those with loose lids. Manufacturing directions provided in this book are particularly detailed about the purging steps, and these should be closely observed.

VI. MICROBIOLOGICAL QUALITY

Microbiological contamination can present significant health hazards in some oral liquids. For example, some oral liquids, such as nystatin suspension, are used in infants and immunocompromised patients, and microbiological contamination with organisms (such as Gram-negative organisms) is not acceptable. There are other oral liquid preparations such as antacids in which *Pseudomonas* sp. contamination is also objectionable. For other oral liquids such as cough preparations, contamination with *Pseudomonas* sp. might not present the same health hazard. However, the presence of a specific *Pseudomonas* sp. may also indicate other plant or raw material contamina-

tion and often points to defects in the water systems and environmental breaches; extensive investigations are often required to trace the source of contamination. Obviously, the contamination of any preparation with Gram-negative organisms is not desirable.

In addition to the specific contaminant being objectionable, such contamination would be indicative of a deficient process as well as an inadequate preservative system. For example, the presence of a *Pseudomonas putida* contaminant could also indicate that *P. aeruginosa*, a similar source organism, is also present.

Because FDA laboratories typically use more sensitive test methods than industry, samples of oral liquids in which manufacturers report microbiological counts well within limits may be found unacceptable by the federal laboratories. This result requires upgrading the sensitivity of testing procedures.

VII. ORAL SUSPENSIONS

Liquid products in which the drug is suspended (not in solution) present some unique manufacturing and control problems. Depending on the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Procedures must therefore be established for filling and diagrams established for line setup prior to the filling equipment.

Good manufacturing practice would warrant testing bottles from the beginning, middle, and end of a batch to ensure that segregation has not occurred. Such samples should not be combined for the purpose of analysis. In-process testing for suspensions might also include an assay of a sample from the bulk tank. More important at this stage, however, may be testing for viscosity.

VIII. PRODUCT SPECIFICATIONS

Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases, dissolution. Viscosity can be important, from a processing aspect, to minimize segregation. In addition, viscosity has also been shown to be associated with bioequivalency. pH may also have some meaning regarding effectiveness of preservative systems and may even have an effect on the amount of drug in solution. With regard to dissolution, there are at least three products that have dissolution specifications. These products include phenytoin suspension, carbamazepine suspension, and sulfamethoxazole and trimethoprim suspension. Particle size is also important, and at this point it would seem that any suspension should have some type of particle size specification. As with other dosage forms, the underlying data to support specifications should be established.

IX. PROCESS VALIDATION

As with other products, the amount of data needed to support the manufacturing process will vary from product to product. Development (data) should have identified critical phases of the operation, including the predetermined specifications that should be monitored during process validation.

For example, for solutions, the key aspects that should be addressed during validation include ensuring that the drug substance and preservatives are dissolved. Parameters such as heat and time should be measured. In-process assay of the bulk solution during or after compounding according to predetermined limits is also an important aspect of process validation. For solutions that are sensitive to oxygen or light, dissolved oxygen levels would also be an important test. Again, the development data and the protocol should provide limits.

As discussed, the manufacture of suspensions presents additional problems, particularly in the area of uniformity. The development data should address the key compounding and filling steps that ensure uniformity. The protocol should provide for the key in-process and finished product tests, along with their specifications. For oral solutions, bioequivalency studies may not always be needed. However, oral suspensions, with the possible exception of some of the over-the-counter antacids, usually require a bioequivalency or clinical study to demonstrate their effectiveness. Comparison of product batches with the biobatch is an important part of the validation process. Make sure there are properly written protocol and process validation reports and, if appropriate, data for comparing full-scale batches with biobatch available during FDA inspection.

X. STABILITY

One area that has presented a number of problems is ensuring the stability of oral liquid products throughout their expiry period. The presence of water or other solvents enhances all reaction rates: Because fluids can contain a certain amount of oxygen, the oxidation reactions are also enhanced, as in the case of vitamins and the phenothiazine class of drugs. Good practice for these classes of drug products should include quantitation of both the active and primary degradant. There should be well-established specifications for the primary degradant, including methods of quantitation of both the active drug and degradant.

Because interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted

to determine whether contact of the drug product with the closure system affects product integrity.

Other problems associated with inadequate closure systems are moisture losses that can cause the remaining contents to become superpotent and microbiological contamination.

XI. PACKAGING

Problems in the packaging of oral liquids have included potency (fill) of unit dose products and accurate calibration of measuring devices such as droppers, which are often provided. For unit dose solution products the label claim quantity within the limits described should be delivered.

Another problem in the packaging of oral liquids is lack of cleanliness of the containers before filling. Fibers and even insects often appear as debris in containers, particularly in the plastic containers used for many of these products. Many manufacturers receive containers shrink-wrapped in plastic to minimize contamination from fiberboard cartons, and many manufacturers use compressed air to clean the containers. Vapors, such as oil vapors, from the compressed air have occasionally been found to present problems, and it is a good practice to use compressed gas from oil-free compressors.

2 Stability Testing of New Drug Substances and Products

I. INTRODUCTION

This chapter describes the principles of study of stability for regulatory filings in the European Union (EU), Japan, and the United States. Details provided here comprise the core stability data package for new drug substances and products and not for abbreviated or abridged applications, variations, or clinical trial applications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. The choice of test conditions is based on an analysis of the effects of climatic conditions, which are described on the basis of the mean kinetic temperature derived from climatic data; thus, the world can be divided into four climatic zones, I–IV.

II. DRUG SUBSTANCE

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help to establish the degradation pathways and the intrinsic stability of the molecule and to validate this stability, indicating the power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. The testing should include the effect of temperature (in 10˚C increments [e.g., 50˚C, 60˚C] above that for accelerated testing), humidity (e.g., 75% relative humidity [RH]) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing; the conditions for photostability testing are described in another chapter.

Examining degradation products under stress conditions is useful in establishing degradation pathways and in developing and validating suitable analytical procedures. However, such examination may not be necessary for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that simulate the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale. Other supporting data can be provided. The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or that simulates the packaging proposed for storage and distribution.

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, should be developed. Stability studies should include testing of those attributes of the drug substance susceptible to change during storage and likely to influence quality, safety, or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes of the drug. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed should depend on the results from validation studies. For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, and 12 months), from a 12-month study is recommended.

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of the studies chosen should be sufficient to cover storage, shipment, and subsequent use. The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case (Table 2.1) should apply if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

TABLE 2.1
General Case

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	25°C ± 2°C, 60% RH ± 5% RH	12
Intermediate	30°C ± 2°C, 60% RH ± 5% RH	6
Accelerated	40°C ± 2°C, 75% RH ± 5% RH	6

Note. RH, relative humidity.

A. General Case

When significant change occurs at any time during 6 months of testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests unless otherwise justified. The initial application should include a minimum of 6 months of data from a 12-month study at the intermediate storage condition. Significant change for a drug substance is defined as failure to meet its specification.

B. Drug Substances Intended for Storage in a Refrigerator

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real-time data available at the long-term storage condition (Table 2.2). If significant change occurs within the first 3 months of testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

TABLE 2.2
Drug Substances Intended for Storage in a Refrigerator

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	5°C ± 3°C	12
Accelerated	25°C ± 2°C, 60% RH ± 5% RH	6

Note. RH, relative humidity.

C. Drug Substances Intended for Storage in a Freezer

For drug substances intended for storage in a freezer, the retest period should be based on the real-time data obtained at long-term storage conditions (Table 2.3). In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing of a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the

TABLE 2.3
Drug Substances Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	–20°C ± 5°C	12

proposed label storage condition (e.g., during shipping or handling).

D. Drug Substances Intended for Storage below –20°C

Drug substances intended for storage below –20°C should be treated on a case-by-case basis. When available long-term stability data on primary batches do not cover the proposed retest period granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the retest period.

Where the submission includes long-term stability data on three production batches covering the proposed retest period, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place at least three additional production batches on long-term stability studies through the proposed retest period.
- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed retest period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches unless otherwise scientifically justified. The purpose of the stability study is to establish, on the basis of testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period. The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95%, one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., $P > .25$ for level of significance of rejection) to the slopes of the regression lines and the zero-time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually, the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data from all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, the batch size, or the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data. Any evaluation should cover not only the assay but also the levels of degradation products and other appropriate attributes.

A storage statement should be established for the labeling in accordance with relevant national and regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, in particular for

drug substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided. A retest period should be derived from the stability information, and a retest date should be displayed on the container label, if appropriate.

III. DRUG PRODUCT

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance, results from stability studies on the drug substance, and experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated. Photostability testing should be conducted on at least one primary batch of the drug product, if appropriate. The standard conditions for photostability testing are described in another chapter.

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and be packaged in the same container closure system proposed for marketing. The manufacturing process used for primary batches should simulate the process that will be applied to production batches and should provide product that is of the same quality and that meets the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches; the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing are applied. Other supporting data can be provided. Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

Specification should be established. Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and that are likely to influence quality, safety, or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes; preservative content (e.g., antioxidant, antimicrobial preservative); and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and indicating stability. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and the release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) — that intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, and 12 months), from a 12-month study is recommended. Reduced designs (i.e., matrixing or bracketing), in which the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability

studies at initial and final time points, and if full shelf-life, long-term data will not be available before submission, at 12 months or at the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case (Table 2.4) should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

TABLE 2.4
General Case

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	25°C ± 2°C, 60% RH ± 5% RH	12
Intermediate	30°C ± 2°C, 60% RH ± 5% RH	6
Accelerated	40°C ± 2°C, 75% RH ± 5% RH	6

Note. RH, relative humidity.

A. General Case

When significant change occurs at any time during 6 months of testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months of data from a 12-month study at the intermediate storage condition.

In general, significant change for a drug product is defined as one or more of the following (as appropriate for the dosage form):

- A 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product's exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for the appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, and dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.
- Failure to meet the acceptance criterion for pH.
- Failure to meet the acceptance criteria for dissolution for 12 dosage units.

B. Drug Products Packaged in Impermeable Containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

C. Drug Products Packaged in Semipermeable Containers

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low-RH environments (Table 2.5). Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

When significant change other than water loss occurs during the 6 months of testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed, as described under the general case, to evaluate the temperature effect at 30°C. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be

TABLE 2.5
Aqueous-Based Drug Products Stored in Semipermeable Containers

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	25°C ± 2°C, 40% RH ± 5% RH	12
Intermediate	30°C ± 2°C, 60% RH ± 5% RH	6
Accelerated	40°C ± 2°C, not more than 25% RH	6

Note. RH, relative humidity.

provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference RH of 40%.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months of storage at 40°C and not more than (NMT) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months of storage at 40°C and NMT 25% RH may be appropriate if justified.

An alternative approach to studying at the reference RH as recommended in Table 2.5 (for either long-term or accelerated testing) is performing the stability studies under higher RH and deriving the water loss at the reference RH through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, by using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

An example of an approach for determining water loss follows:

> For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference RH is to multiply the water loss rate measured at an alternative RH at the same temperature by a water loss rate ratio, shown in Table 2.6. A linear water loss rate at the alternative RH over the storage period should be demonstrated. For example, at a given temperature (e.g., 40°C), the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3.0 — the corresponding water loss rate ratio.

Valid water loss rate ratios at RH conditions other than those shown in Table 2.6 can also be used.

TABLE 2.6
Determining Water Loss

Alternative Relative Humidity (%)	Reference Relative Humidity (%)	Ratio of Water Loss Rates at a Given Temperature
60	25	1.9
60	40	1.5
75	25	3.0

D. Drug Products Intended for Storage in a Refrigerator

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss. Data from refrigerated storage should be assessed according to details given below (Table 2.7).

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real-time data available from the long-term storage condition. If significant change occurs within the first 3 months of testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipment and handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

TABLE 2.7
Drug Products Intended for Storage in a Refrigerator

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	5°C ± 3°C	12
Accelerated	25°C ± 2°C, 60% RH ± 5% RH	6

Note. RH, relative humidity.

E. Drug Products Intended for Storage in a Freezer

For drug products intended for storage in a freezer, the shelf life should be based on the real-time data obtained at the long-term storage condition (Table 2.8). In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

TABLE 2.8
Drug Products Intended for Storage in a Freezer

Study	Storage Condition	Minimum Time Period Covered by Data at Submission (months)
Long-term	–20°C ± 5°C	12

F. Drug Products Intended for Storage below –20°C

Drug products intended for storage below –20°C should be treated on a case-by-case basis. When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months and to place at least three additional production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.
- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches unless otherwise scientifically justified. Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

A systematic approach should be adopted in the presentation and evaluation of the stability information, incorporating, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product,

a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., $P > .25$ for level of significance of rejection) to the slopes of the regression lines and zero-time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, the batch size, or the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided. There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

IV. GLOSSARY

Accelerated Testing — Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions, such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing — The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic Zones — The four zones in the world that are distinguished by their characteristic, prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196–202, 1985 and 29:39–47, 1986).

Commitment Batches — Production batches of a drug substance or drug product for which the stability studies are initiated or completed postapproval through a commitment made in the registration application.

Container Closure System — The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage Form — A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug sub-

stance generally, but not necessarily, in association with excipients.

Drug Product — The dosage form in the final immediate packaging intended for marketing.

Drug Substance — The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient — Anything other than the drug substance in the dosage form.

Expiration Date — The date placed on the container label of a drug product designating the time before which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Formal Stability Studies — Long-term and accelerated (and intermediate) studies undertaken on primary or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable Containers — Containers that provide a permanent barrier to the passage of gases or solvents (e.g., sealed aluminum tubes for semisolids, sealed glass ampoules for solutions).

Intermediate Testing — Studies conducted at 30˚C/60% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long-term at 25˚C.

Long-Term Testing — Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.

Mass Balance — The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing — The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as covering, for example, different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

Mean Kinetic Temperature — A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation. When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes *(J. Pharm. Sci.* 60:927–929, 1971) can be used.

New Molecular Entity — An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or noncovalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot Scale Batch — A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production–scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is larger.

Primary Batch — A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot-scale batch. For a drug product, two of the three batches should be at least pilot-scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production Batch — A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest Date — The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest Period — The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semipermeable Containers — Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through

the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene pouches for large volume parenterals, as well as low-density polyethylene ampoules, bottles, and vials.

Shelf Life (also referred to as Expiration Dating Period) — The time period during which a drug product is expected to remain within the approved shelf-life specification, provided that it is stored under the conditions defined on the container label.

Specification — See International Conference on Harmonization (ICH) Q6A and ICH Q6B.

Specification, Release — The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification, Shelf Life — The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage Condition Tolerances — The acceptable variations in temperature and RH of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes caused by opening of doors of the storage facility are accepted as unavoidable. The effect of excursions resulting from equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress Testing (drug substance) — Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress Testing (drug product) — Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting Data — Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

REFERENCES

ICH guidelines are available at http:/www.fda.gov/guidance

ICH Q1B Photostability Testing of New Drug Substances and Products (November 1996)

ICH Q1C Stability Testing for New Dosage Forms (November 1996)

ICH Q3A Impurities in New Drug Substances (January 1996)

ICH Q3B Impurities in New Drug Products (November 1996)

ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (July 1996)

ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (December 2000)

ICH Q6B Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products (August 1999)

3 Container Closure Systems

I. INTRODUCTION

According to the Federal Food, Drug, and Cosmetic Act (the Act), Section 501(a)(3), a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health." In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the Act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs. Section 505(b)(1)(D) of the Act states that an application shall include a full description of the methods used in the manufacturing, processing, and packing of such drug. This includes facilities and controls used in the packaging a drug product.

A. Definitions

Materials of construction are the substances (e.g., glass, high-density polyethylene [HDPE] resin, metal) used to manufacture a packaging component. A packaging component is any single part of a container closure system. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals), overwraps, administration accessories, and container labels. A primary packaging component is a packaging component that is or may be in direct contact with the dosage form. A secondary packaging component is a packaging component that is not and will not be in direct contact with the dosage form.

A container closure system is the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

A package, or market package, is the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink-wrap). A market package is the article provided to a pharmacist or retail customer on purchase and does not include packaging used solely for the purpose of shipping such articles.

The term "quality" refers to the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use. In this guidance, the term is also understood to convey the properties of safety, identity, strength, quality, and purity (see Title 21 Code of Federal Register (CFR) 211.94(a)).

An extraction profile is the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A quantitative extraction profile is one in which the amount of each detected substance is determined.

B. Current Good Manufacturing Practice, the Consumer Product Safety Commission, and Requirements on Containers and Closures

Current good manufacturing practice requirements for the control of drug product containers and closures are included in 21 CFR Parts 210 and 211. The U.S. Food and Drug Administration (FDA) requirement for tamper-resistant closures is included in 21 CFR 211.132 and the Consumer Product Safety Commission requirements for child-resistant closures are included in 16 CFR 1700.

The United States Pharmacopeial Convention has established requirements for containers that are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary*. For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well-closed, or light-resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the USP. The requirements for materials of construction are defined in the "General Chapters" of the USP.

C. Additional Considerations

The packaging information in the chemistry, manufacturing, and controls section of an Investigational New Drug Application (IND) usually includes a brief description of the components, the assembled packaging system, and any precautions needed to ensure the protection and preservation of the drug substance and drug product during their use in the clinical trials.

A contract packager is a firm retained by the applicant to package a drug product. The applicant remains responsible for the quality of the drug product during shipping,

storage, and packaging. The information regarding the container closure system used by a contract packager that should be submitted in the Chemistry, Manufacturing, and Control (CMC) section of an application (New Drug Application [NDA], Abbreviated New Drug Application [ANDA], or Biological License Application [BLA]), or in a Drug Master File (DMF) that is referenced in the application, is no different from that which would be submitted if the applicant performed its own packaging operations. If the information is provided in a DMF, then a copy of the letter of authorization for the DMF should be provided in the application.

II. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show that each proposed container closure system and its components are suitable for its intended use.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, as a liquid-based dosage form is more likely to interact with the packaging components. There is a correlation between the degree of concern regarding the route of administration and the likelihood of packaging component–dosage form interactions for different classes of drug products:

Highest: inhalation, aerosols, sterile powders, and solutions; powders for injections and injection; inhalation, injectable, powders, suspensions

High: ophthalmic solutions and suspensions, transdermal ointments and patches, nasal aerosols and sprays

Low: topical solutions and topical powders; oral tablets and oral suspensions; topical oral powders (hard and soft and lingual aerosols; gelatin), capsules, oral solutions, and suspensions

"Suitability" refers to the tests and studies used and accepted for the initial qualification of a component, or a container closure system, for its intended use. "Quality control" refers to the tests typically used and accepted to establish that, after the application is approved, the components and the container closure system continue to possess the characteristics established in the suitability studies. The subsections on associated components and secondary components describe the tests and studies for establishing suitability and quality control for these types of components. However, the ultimate proof of the suitability of the container closure system and the packaging process is established by full shelf-life stability studies.

Every proposed packaging system should be shown to be suitable for its intended use: It should adequately protect the dosage form, it should be compatible with the dosage form, and it should be composed of materials that are considered safe for use with the dosage form and the route of administration. If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to function properly. Information intended to establish suitability may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the firm. An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided. The information may be submitted directly in the application or indirectly by reference to a DMF. If a DMF is used, a letter authorizing reference (i.e., letter of authorization) to the DMF must be included in the application.

A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a degradation in the quality of that dosage form over its shelf life. Common causes of such degradation are exposure to light, loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth.

Not every drug product is susceptible to degradation by all of these factors: not all drug products are light sensitive. Not all tablets are subject to loss of quality caused by absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The test for light transmission (USP <661>) is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the monograph recommendation. A firm, therefore, may want to consider using additional or alternate measures to provide light protection for these drug products when necessary.

Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., because of the buildup of pressure during storage). Leaks can also occur in tubes as a result of failure of the crimp seal. Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface (e.g., the wall of a low-density polyethylene [LDPE] bottle) or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection, because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

Protection from microbial contamination is provided by maintaining adequate container integrity after the packaging system has been sealed. An adequate and validated procedure should be used for drug product manufacture and packaging.

Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component. Examples of interactions include loss of potency, caused by absorption or adsorption of the active drug substance, or degradation of the active drug substance, induced by a chemical entity leached from a packaging component; reduction in the concentration of an excipient caused by absorption, adsorption, or leachable-induced degradation; precipitation; changes in drug product pH; discoloration of either the dosage form or the packaging component; or increase in brittleness of the packaging component.

Some interactions between a packaging component and dosage form will be detected during qualification studies on the container closure system and its components. Others may not show up except in the stability studies. Therefore, any change noted during a stability study that may be attributable to interaction between the dosage form and a packaging component should be investigated, and appropriate action should be taken, regardless of whether the stability study is being conducted for an original application, a supplemental application, or as fulfillment of a commitment to conduct postapproval stability studies.

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product. This consideration is especially important for those packaging components that may be in direct contact with the dosage form, but it is also applicable to any component from which substances may migrate into the dosage form (e.g., an ink or adhesive). Making the determination that a material of construction used in the manufacture of a packaging component is safe for its intended use is not a simple process, and a standardized approach has not been established. There is, however, a body of experience that supports the use of certain approaches that depend on the route of administration and the likelihood of interactions between the component and the dosage form. For a drug product such as an injection, inhalation, ophthalmic, or transdermal product, a comprehensive study is appropriate. This involves two parts: first, an extraction study on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration), and second, a toxicological evaluation of those substances that are extracted to determine the safe level of exposure via the label-specified route of administration. This technique is used by the Center for Food Safety and Applied Nutrition to evaluate the safety of substances that are proposed as indirect food additives (e.g., polymers or additives that may be used in for packaging foods).

The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and should take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). For many injectable and ophthalmic drug products, data from the Biological Reactivity Tests and Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.

For many solid and liquid oral drug products, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) promulgated by Center for Food Safety and Applied Nutrition for the materials of construction used in the packaging component will typically be considered sufficient. Although these regulations do not specifically apply to materials for packaging drug products, they include purity criteria and limitations pertaining to the use of specific materials for packaging foods that may be acceptable for the evaluation of drug product packaging components. Applicants are cautioned that this approach may not be acceptable for liquid oral dosage forms intended for chronic use.

For drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety. Performance of the container closure system refers to its ability to function in the manner for which it was designed. A container closure system is often called on to do more than simply contain the dosage form. When evaluating performance, two major considerations are container closure system functionality and drug delivery.

First, consider container closure system functionality: the container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g. a prefilled syringe), or have other functions.

The second consideration is drug delivery: Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

Container closure system functionality or drug delivery are compromised when the packaging system fails to operate as designed. Failure can result from misuse, faulty design, manufacturing defect, improper assembly, or wear and tear during use. Tests and acceptance criteria regarding dosage form delivery and container closure system functionality should be appropriate to the particular dosage form, route of administration, and design features. If there is a special performance function built into the drug product (e.g., a counter cap), it is of importance for any dosage form or route of administration to show that the container closure system performs that function properly.

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to ensure consistency in the packaging components. These controls are intended to limit unintended postapproval variations in the manufacturing procedures or the materials of construction for a packaging component and to prevent adverse effects on the quality of a dosage form.

Principal consideration is usually given to consistency in physical characteristics and chemical composition. The physical characteristics of interest include dimensional criteria (e.g., shape, neck finish, wall thickness, design tolerances), physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., metering valve delivery volume or the ease of movement of syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect package permeability, drug delivery performance, or the adequacy of the seal between the container and the closure. Variation in any physical parameter is considered important if it can affect the quality of a dosage form.

The chemical composition of the materials of construction may affect the safety of a packaging component. New materials may result in new substances being extracted into the dosage form or in a change in the amount of known extractables. Chemical composition may also affect the compatibility, functional characteristics, or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability). A composition change may occur as a result of a change in formulation or a change in a processing aid (e.g., using a different mold release agent) or through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than is a change in the supplier of a pure chemical compound, because polymeric and natural materials are often complex mixtures. A composition change may also occur with a change in the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), different equipment, or both. A change in formulation is considered a change in the specifications for the packaging component. Changes in the formulation of a packaging component by its manufacturer should be reported to the firm that purchases that component and to any appropriate DMF. The firm that purchases the component should, in turn, report the change to its application as required under 21 CFR 314.70(a) or 601.12. Manufacturers who supply a raw material or an intermediate packaging component should inform their customers of any intended changes to formulations or manufacturing procedures and should update the DMF in advance of implementing such a change. Changes that seem innocuous may have unintended consequences on the dosage form marketed in the affected packaging system.

The use of stability studies for monitoring the consistency of a container closure system in terms of compatibility with the dosage form and the degree of protection provided to the dosage form is accepted. At present, there is no general policy concerning the monitoring of a packaging system and components with regard to safety. One exception involves inhalation drug products, for which batch-to-batch monitoring of the extraction profile for the polymeric and elastomeric components is routine.

"Associated components" are packaging components that are typically intended to deliver the dosage form to the patient but that are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container on opening or used only when a dose is to be administered. Measuring spoons, dosing cups, measuring syringes, and vaginal delivery tubes are examples of associated components that typically contact the dosage form only during administration. A hand pump or dropper combined into a closure are examples of an associated component that would contact the dosage form from the time the packaging system is opened until the dosing regimen is completed.

The complete and assembled component and its parts should meet suitability criteria appropriate for the drug product and the actual use of the component. Safety and functionality are the most common factors to be established for suitability. The length of time that the associated component and the dosage form are in direct contact should also be taken into consideration when assessing the suitability of an associated component.

Unlike primary and associated packaging components, secondary packaging components are not intended to make contact with the dosage form. Examples are cartons, which are generally constructed of paper or plastic, and overwraps, which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic, or paper. A secondary packaging component generally provides one or more of the following additional services:

- Protection from excessive transmission of moisture or solvents into or out of the packaging system
- Protection from excessive transmission of reactive gases (atmospheric oxygen, inert headspace filler gas, or other organic vapors) into or out of the packaging system
- Light protection for the packaging system
- Protection for a packaging system that is flexible or that needs extra protection from rough handling
- Additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the packaging system from microbial intrusion)

When information on a container closure system is submitted in an application, the emphasis would normally be on the primary packaging components. For a secondary packaging component, a brief description will usually suffice unless the component is intended to provide some additional measure of protection to the drug product. In this case, more complete information should be provided, along with data showing that the secondary packaging component actually provides the additional protection.

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component or from a volatile substance present in the secondary packaging component. (For example, a solution packaged in an LDPE container was found to be contaminated by a volatile constituent of the secondary packaging components that enclosed it.) In such a case, the secondary packaging component should be considered a potential source of contamination, and the safety of its materials of construction should be taken into consideration.

A. Description

A general description of the entire container closure system should be provided in the CMC section of the application. In addition, the following information should be provided by the applicant for each individual component of the packaging system:

Identification by product name, product code (if available), name and address of the manufacturer, and a physical description of the packaging component (e.g., type, size, shape, and color)

Identification of the materials of construction (i.e., plastics, paper, metal, glass, elastomers, coatings, adhesives, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer); alternate materials of construction should be indicated; postconsumer recycled plastic should not be used in the manufacture of a primary packaging component, and if it is used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately

Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation)

B. Information about Suitability

To establish safety and to ensure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component. Test results from appropriate qualification and characterization tests should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should be also provided.

To address protection, use of tests (see Attachment A) for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. Testing for properties other than those described above (e.g., gas transmission, solvent leakage container integrity) may also be necessary.

To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and to introduce extracted substances into the patient. For drug products less likely to interact, other tests (e.g., Biological Reactivity Test) or information (e.g., appropriate reference to the indirect food additive regulations at 21 CFR 174-186) could be used to address the issue of safety and compatibility. For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product.

To address performance, the results of nonfunctionality tests are considered sufficient if the test and acceptance criteria are appropriate for the intended purpose. Tests described there are typically considered sufficient standards for establishing specified properties and characteristics of specified materials of construction or packaging components. For nonfunctionality tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test for its intended use and its validation.

Testing on an assembled container closure system is usually performed by the applicant (or a testing laboratory commissioned by the applicant), and the test results are provided in the application. Such tests may include vacuum-leak testing, moisture permeation, and weight loss or media fill. Testing on an individual packaging component is typically performed by the manufacturer of the component and is reported via a DMF (see Section V).

The fabricator/manufacturer of a packaging component and the drug product manufacturer who uses this firm share the responsibility for ensuring the quality of packaging components. These firms should have a quality control program in place so that consistent components are produced. The drug product manufacturer must have an inspection program for incoming packaging components and materials (21 CFR 211.22, 211.84 and 211.122). For most drug products, a drug product manufacturer may accept a packaging component lot based on receiving a Certificate of Analysis (COA) or Certificate of Certification (COC) from the component supplier and on the performance of an appropriate identification test, provided the supplier's test data are periodically validated (21 CFR 211.84(d)(3)). Acceptance of a packaging component lot based on a supplier's COA or COC may not be appropriate in all cases (e.g., some packaging components for certain inhalation drug products).

The tests and methods used by the applicant for acceptance of each batch of a packaging component that they receive should be described. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria. Acceptance criteria for extractables should also be included, if appropriate.

Dimensional and performance criteria should be provided. Dimensional information is frequently provided via a detailed schematic drawing, complete with target dimensions and tolerances, and it may be provided via the packaging component manufacturer's DMF. A separate drawing may not be necessary if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

Each manufacturer of a packaging component sold to a drug product manufacturer should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the component. These measures generally include release criteria (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of the packaging component is based on statistical process control, a complete description of the process (including control criteria) and its validation should be provided.

The description of the manufacturing process is generally brief and should include any operations performed on the packaging component after manufacture but before shipping (e.g., washing, coating, or sterilization). In some cases it may be desirable for the description to be more detailed and to include in-process controls. This information may be provided via a DMF.

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or in part on the quality control procedures of a manufacturer who makes an intermediate packaging component that is used to create the component. If so, each contributor to the final packaging system should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the separate components and of the assembled packaging system that they provide.

The manufacturer of each material of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their product. This information may be provided via a DMF.

C. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container closure systems proposed in the application. The packaging system used in each stability study should be clearly identified, and the container closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. Even when a formal test for quality of the packaging system is not performed, the applicant should investigate any observed change in the packaging system used in the stability studies. The observations, results of the investigation, and corrective actions should be included in the stability report. If the corrective action requires a change in an approved container closure system, a supplemental application should be submitted.

D. Inhalation Drug Products

Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory tract-compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient.

E. Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and that all are required to be sterile. Injectable dosage forms represent one of the highest-risk drug products. Any contaminants present (as a result of contact with a packaging component or caused by the packaging system's failure to provide adequate protection) can be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals if they have a solution volume of 100 mL or less, or as large-volume parenterals if the solution volume exceeds 100 mL. For solids that must be dissolved or dispersed in an appropriate diluent before being injected, the diluent may be in the same container closure system (e.g., a two-part vial) or be part of the same market package (e.g., a kit containing a vial of diluent). A small-volume parenteral may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampule, or a flexible bag. A large-volume parenteral may be packaged in a vial, a flexible bag, a glass bottle, or in some cases, as a disposable syringe.

Cartridges, syringes, vials, and ampules are usually composed of Type I or II glass or of polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. The input (medication) and output (administration) ports for flexible bags may be plastic or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible packaging system from rough handling.

The potential effects of packaging component/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity, and pyrogenic effects may result from the presence of impurities. The potency of the drug product or the concentration of the antimicrobial preservatives may decrease because of adsorption or absorption. A cosolvent system essential to the solubilization of a poorly soluble drug can also serve as a potent extractant of plastic additives. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material.

Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or from exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, whereas sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of elastomeric closures for injections will typically be considered sufficient evidence of safety. For plastic components, data from Biological Reactivity Tests will typically be considered sufficient evidence of safety. Whenever possible, the extraction studies should be performed using the drug product. If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., because of high or low pH or a solubilizing excipient), then drug product should be used as the extracting medium. If the drug substance significantly affects extraction characteristics, it may be necessary to perform the extractions using the drug product vehicle. If the total of the extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. It may be advisable to obtain a quantitative extraction profile of an elastomeric or plastic packaging component and to compare this periodically to the profile from a new batch of the packaging component. Extractables should be identified whenever possible. For a glass packaging component, data from *Containers: Chemical Resistance — Glass Containers* will typically be considered sufficient evidence of safety and compatibility. In some cases (e.g., for some chelating agents), a glass packaging component may need to meet additional criteria to ensure the absence of significant interactions between the packaging component and the dosage form.

Performance of a syringe is usually addressed by establishing the force to initiate and maintain plunger movement down the barrel and the capability of the syringe to deliver the labeled amount of the drug product.

These drug products are usually solutions marketed in a LDPE bottle with a dropper built into the neck (sometimes referred to as droptainer) or ointments marketed in a metal tube with an ophthalmic tip. A few solution products use a glass container because of stability concerns

regarding plastic packaging components. Ophthalmic ointments that are reactive toward metal may be packaged in a tube lined with an epoxy or vinyl plastic coating. A large-volume intraocular solution (for irrigation) may be packaged in a glass or polyolefin (polyethylene or polypropylene) container. The American Academy of Ophthalmology recommended to the FDA that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system.

Although ophthalmic drug products can be considered topical products, they have been grouped here with injectables because they are required to be sterile (21 CFR 200.50(a)(2)) and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product. Because ophthalmic drug products are applied to the eye, compatibility and safety should also address the container closure system's potential to form substances which irritate the eye or introduce particulate matter into the product (see USP <771> Ophthalmic Ointments).

F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products falls into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms to be slower than for aqueous solutions. Because of extended contact, the amount of leachables in these drug products may depend more on a leachable material's affinity for the liquid/semisolid phase than on the rate of migration.

Typical liquid-based oral dosage forms are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions. These products are usually nonsterile but may be monitored for changes in bioburden or for the presence of specific microbes. These dosage forms are generally marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups. The dosage form may be used as is or admixed first with a compatible diluent or dispersant. A bottle is usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. A pouch may be a single-layer plastic or a laminated material. Both bottles and pouches may use an overwrap, which is usually a laminated material. A single-dose cup may be metal or plastic with a heat-sealed lid made of a laminated material.

A liquid-based oral drug product typically needs to be protected from solvent loss, microbial contamination, and sometimes, from exposure to light or reactive gases (e.g., oxygen). For glass components, data showing that a component meets the requirements of *Containers: Glass Containers* are accepted as sufficient evidence of safety and compatibility. For LDPE components, data from Containers tests are typically considered sufficient evidence of compatibility. The General Chapters do not specifically address safety for polyethylene (HDPE or LDPE), polypropylene, or laminate components. A patient's exposure to substances extracted from a plastic packaging component (e.g. HDPE, LDPE, polypropylene, laminated components) into a liquid-based oral dosage form is expected to be comparable to a patient's exposure to the same substances through the use of the same material when it is used to package food. On the basis of this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174-186) is typically considered sufficient to establish safety of the material of construction, provided any limitations specified in the regulations are taken into consideration. This assumption is considered valid for liquid-based oral dosage forms that the patient will take only for a relatively short time (acute dosing regimen). For liquid-based oral drug products that the patient will continue to take for an extended period (i.e., months or years [chronic drug regimen]), a material of construction that meets the requirements for indirect food additives will be considered safe — on that basis alone — only if the patient's exposure to extractables can be expected to be no greater than the exposure through foods or if the length of exposure is supported by toxicological information. For example, if the dosage form is aqueous-based and contains little or no cosolvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), meeting the requirements of the indirect food additive regulations will usually satisfy the issue of safety.

If the dosage form contains cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), then additional extractable information may be needed to address safety issues. Performance is typically not a factor for liquid-based oral drug products.

Topical dosage forms include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions, and suspensions. These dosage forms are generally intended for local (not systemic) effect and are generally applied to the skin or oral mucosal surfaces. Topical products also include some nasal and otic preparations as well as some ophthalmic drug products. Vaginal and rectal drug products may be considered to be topical if they are

intended to have a local effect. Some topical drug products are sterile or may be subject to microbial limits. In these cases, additional evaluation may be necessary when determining the appropriate packaging.

A liquid-based topical product typically has a fluid or semisolid consistency and is marketed in a single- or multiple-unit container (e.g., a rigid bottle or jar, a collapsible tube, or a flexible pouch). A powder product may be marketed in a sifter-top container. An antibacterial product may be marketed as part of a sterile dressing; there are also a number of products marketed as a pressurized aerosol or a hand-pumped spray. A rigid bottle or jar is usually made of glass or polypropylene with a screw cap. The same cap liners and inner seals are sometimes used as with solid oral dosage forms. A collapsible tube is usually constructed from metal—or is metal-lined, from LDPE, or from a laminated material. Tubes are identified as either blind-end or open-end. In the former, there is no product contact with the cap on storage. Usually, the size of the tube is controlled by trimming it to an appropriate length for the target fill volume. Fill volume is commonly determined as an in-process measurement, using bulk density. Usually there is no cap liner, although the tube may have a liner. Aluminum tubes usually include a liner. A tube liner is frequently a lacquer or shellac whose composition should be stated. A tube is closed by folding or crimping the open end. The type of fold (roll or saddle) should be described, as well as the type and composition of any sealant. If the tube material is self-sealing through the application of heat alone, this should be stated. If the market package includes a separate applicator device, this should be described. Product contact is possible if the applicator is part of the closure, and therefore, an applicator's compatibility with the drug product should be established as appropriate. Dressings consist of dosage form on a bandage material (e.g., absorbent gauze or gauze bandage) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Topical aerosols are not intended to be inhaled; therefore, the droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin (topical aerosol) or mouth (lingual aerosol), and functionality of the sprayer should be addressed. A topical aerosol may be sterile or may conform to acceptance criteria for microbial limits. The packaging system for a liquid-based topical product should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of the materials of construction for the packaging components should be evaluated. For solid dosage forms, an appropriate reference to the indirect food additive regulations is typically considered sufficient to establish safety.

Topical delivery systems are self-contained, discrete dosage forms that are designed to deliver drug via intact skin or body surface. There are three types of topical delivery systems: transdermal, ocular, and intrauterine.

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for 7 days. Intrauterine systems are held in place without adhesive and may stay in place for a year. A transdermal system usually comprises an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be constructed of a plastic material impregnated with active ingredients or a coated metal. It is shaped to remain in place after being inserted in the uterus. Each of these systems is generally marketed in a single-unit soft blister pack or a preformed tray with a preformed cover or overwrap.

Compatibility and safety for topical delivery systems are addressed in the same manner as for topical drug products. Performance and quality control should be addressed for the rate-controlling membrane. Appropriate microbial limits should be established and justified for each delivery system. Microbiological standards are under development; therefore, the review division for a specific application should be consulted.

G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. Powders that are reconstituted in their market container, however, have an additional possibility of an interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared with the component/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility and safety of the container closure system are being evaluated.

A typical container closure system is a plastic (usually HDPE) bottle with a screw-on or snap-off closure and a flexible packaging system, such as a pouch or a blister package. A typical closure consists of a cap — often with a liner — frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.

The most common forms of flexible packaging are the blister package and the pouch. A blister package usually consists of a lid material and a forming film. The lid material is usually a laminate, which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side.

The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate that is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.

Solid oral dosage forms generally need to be protected from the potential adverse effects of water vapor. Protection from light and reactive gases may also be needed. For example, the presence of moisture may affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form. The container should have an intrinsically low rate of water vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

1. Polyethylene Containers (USP <661>)

This test is conducted on containers heat-sealed with foil laminate; therefore, only the properties of the container are evaluated. The level of protection from water vapor permeation provided by a packaging system marketed with a heat-sealed foil laminate inner seal (up to the time the inner seal is removed) is expected to be approximately the same as that determined by this test. The acceptance criteria are those established in USP <671>.

2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>)

This test measures the water vapor permeation of a single-unit or unit-dose container closure system and establishes acceptance criteria for five standards (Class A–E containers).

3. Multiple-Unit Containers for Capsules and Tablets (USP <671>)

This test is intended for drugs being dispensed on prescription, but it has also been applied to the drug product manufacturer's container closure system. If the container closure system has an inner seal, it should be removed before testing. The results from this study reflect the contributions to water vapor permeation through the container and through the seal between the container and the closure. Acceptance criteria have been established for two standards (tight containers and well-closed containers).

For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect food additive regulations as evidence of safety for the materials of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirements of the Containers test.

The monographs for Purified Cotton and Purified Rayon USP will typically be considered sufficient standards to establish the safety of these materials as fillers in the packaging of tablets or capsules, with the following caveats: cotton need not meet the monograph requirements for sterility, fiber length, or absorbency; and rayon need not meet the monograph requirements for fiber length or absorbency. Appropriate tests and acceptance criteria for identification and for moisture content should be provided for both cotton and rayon filler. Rayon has been found to be a potential source of dissolution problems for gelatin capsules and gelatin-coated tablets, and this characteristic should be considered when choosing filler. The use of other fillers may be considered with appropriate tests and acceptance criteria. If a desiccant or other absorbent material is used, the composition should be provided (or an appropriate DMF referenced). The component should differ in shape or size from the tablets or capsules with which it is packaged. This will help distinguish between the component and the dosage form. Because these are considered primary packaging components, appropriate tests and acceptance criteria to establish suitability should be provided.

H. Other Dosage Forms

The current good manufacturing practice requirements for container closure systems for compressed medical gases are described in 21 CFR 210 and 211. The containers are regulated by the U.S. Department of Transportation. When submitting information for a drug product or dosage form not specifically covered by the sections above, a firm should take into consideration the compatibility and safety concerns raised by the route of administration of the drug product and the nature of the dosage form (e.g., solid or liquid-based); the kinds of protection the container closure system should provide to the dosage form; and the potential effect of any treatment or handling that may be unique to the drug product in the packaging system. Quality control procedures for each packaging component should ensure the maintenance of the safety and quality of future production batches of the drug product.

III. POSTAPPROVAL PACKAGING CHANGES

For an approved application (NDA, ANDA, or BLA), a change to a container closure system, to a component of the container closure system, to a material of construction for a component, or to a process involving one of the above must be reported to the application. The filing requirements are specified under 21 CFR 314.70 (supplements and other changes to an approved application) for an NDA or ANDA, and under 21 CFR 601.12 (changes to an approved application) for a BLA.

IV. TYPE III DRUG MASTER FILES

The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA, or BLA, or with the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is considered proprietary) may be placed in a Type III DMF and incorporated into the application by a letter from the manufacturer to the applicant that authorizes reference to the DMF. The letter of authorization should specify the firm to whom authorization is granted, the component or material of construction being described, and where the information or data is located in the file by page number or date of submission. This last item is especially important for files that contain information on multiple components or have several volumes. Information in a Type III DMF is not restricted to data of a proprietary nature. DMF holders may include in their files as much or as little information as they choose. In addition, a manufacturer of a packaging component is not required to maintain a Type III DMF. Without a DMF, there is no procedure for the FDA to review proprietary information except by submission to the application.

The FDA ordinarily reviews a DMF only in connection with an application (IND, NDA, ANDA, or BLA). If the combined information from the application and the DMF is not adequate to support approval of the application or safety for the IND, then the agency may request additional information from the applicant or the DMF holder, as appropriate.

In the event of a change in the DMF, the holder of a DMF must notify the holder of each application supported by the DMF (21 CFR 314.420(c)). Notice should be provided well before the change is implemented to allow the applicant or sponsor enough time to file a supplement or an amendment to the affected application.

V. BULK CONTAINERS

Drug substances are generally solids, but some are liquids or gases. The container closure system for storage or shipment of a bulk solid drug substance is typically a drum with double LDPE liners that are usually heat sealed or closed with a twist tie. A desiccant may be placed between the bags.

The drum provides protection from light and mechanical strength to protect the liner during shipment and handling. The majority of the protection from air and moisture is provided by the liner. Because LDPE is not a particularly good moisture barrier, a drug substance that is moisture sensitive may need additional protection. An alternative to a LDPE bag is a heat-sealable laminate bag with a comparatively low rate of water vapor transmission.

Qualification of the packaging system is usually based on establishing compatibility and safety of the liner but may also include characterization for solvent or gas transmission. The container closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal container with a rugged, tamper-resistant closure. Qualification of the container closure system may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate.

The application (or Type II DMF) should include a detailed description of the complete container closure system for the bulk drug substance as well as a description of the specific container, closure, all liners, inner seal, and desiccant (if any), and a description of the composition of each component. A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction. The tests, methods, and criteria for the acceptance and release of each packaging component should be provided. Stability studies to establish a retest period for bulk drug substance in the proposed container closure system should be conducted with fillers or desiccant packs in place (if used). Smaller versions that simulate the actual container closure system may be used.

A container closure system for bulk drug products may be used for storage before packaging or for shipment to repackagers or contract packagers. In all cases, the container closure system should adequately protect the dosage form and should be constructed of materials that are compatible and safe. Container closure systems for on-site storage have generally been considered a current good manufacturing practice issue under 21 CFR 211.65. However, if a firm plans to hold bulk drug products in

storage, then the container closure system and the maximum storage time should be described and justified in the application. In addition, stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage form. Even when the storage time before packaging will be short, a firm should use a container closure system that provides adequate protection and that is manufactured from materials that are compatible and safe for the intended use.

A container closure system for the transportation of bulk drug products to contract packagers should be described in the application. The container closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with product being stored, and be safe for the intended use. The protective properties of the shipping container are verified by the practice of including annual batches of the packaged product in postapproval stability studies.

A container closure system specifically intended for the transportation of a large volume of drug product to a repackager, whether for a solid or liquid dosage form, is considered a market package. The package should meet the same requirements for protection, compatibility, and safety as a smaller market package; should be included in the stability studies for application approval and in the long-term stability protocol; and should be fully described in the application. The length of time that the dosage form will spend in the bulk container may be a factor in determining the level of detail of the supporting information. Two examples of a large-volume shipping package are a 10,000-tablet HDPE pail with tamper-evident closure and a 10-L polyethylene terephthalate container with a screw-cap closure with dispenser attachment for a liquid drug product. Both are intended for sale to a mass distribution pharmacy.

REFERENCES

FDA guidelines are available at http://www.fda.gov/guidance.

Compressed Medical Gases Guideline (February 1989)

FDA Guideline for Drug Master Files (September 1989)

FDA Guidance for Industry on the Submission of Documentation for the Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994)

FDA Guidance for Industry on the Content and Format on Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products (November 1995)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for *In Vivo* Use (August 1996)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products (January 1997)

FDA Guidance for the Photostability Testing of New Drug Substance and Products (May 1997)

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances (January 1998)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Vaccine or Related Product (January 1999)

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products (February 1999)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Biological *In Vitro* Diagnostic Product (March 1999)

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for Allergenic Extract or Allergen Patch Test (April 1999)

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (May 1999)

4 Preapproval Inspections

I. INTRODUCTION

A preapproval inspection is a visit by regulatory authority inspectors (generally from the District officer of FDA) to review the compliance, in terms of adequacy and accuracy of the information included in a regulatory submission (Compliance Program Guidance Manual, Program 7346.832). The preapproval inspection program has evolved over the years in response to the fraudulent submissions to the U.S. Food and Drug Administration (FDA) by the the generic drug industry.

A. Background

The Food, Drug, and Cosmetic Act provides that the FDA may approve a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity. The applicant is required to submit information in the NDA/ANDA to the Center for Drug Evaluation and Research (CDER), which contains among other things a method of analysis and details as to how the firm proposes to manufacture — and control the manufacture — of the product that is the subject of the application. This information is reviewed by CDER scientists (chemists, microbiologists, etc.) to determine whether the specifications in the application meet the FDA's standards. The CDER's role in the preapproval process is to review data submitted to the agency as part of premarket NDAs and generic drug applications and to establish specifications for the manufacture and control of the resulting drug product on the basis of the submitted data.

The investigator's role is to ensure current good manufacturing practice (cGMP) compliance, verify the authenticity and accuracy of the data contained in these applications, and report any other data that may affect the firm's ability to manufacture the product in compliance with GMPs. This program is designed to provide close inspectional and analytical attention to the authenticity and accuracy of data in applications and to provide information regarding facilities. Such coverage is necessary to ensure that applications are not approved if the applicant has not demonstrated an ability to operate with integrity and in compliance with all applicable requirements.

B. Objective

The objective of the compliance program is to ensure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and new drug substances are audited

1. Through on-site inspections for compliance with cGMPs
2. For conformance with application commitments
3. To ensure data is authentic and accurate
4. Through laboratory testing of products, including evaluations of the adequacy of analytical methodology

Both foreign and domestic establishments are covered by this program. Such coverage is intended to be consistent to the extent possible. This program provides guidance for establishment inspections and related investigations and for laboratory evaluations of methods of analysis proposed by applicants in NDA and ANDA submissions.

Before any application is approved by the CDER, a determination will be made of whether all establishments that will participate in the manufacture, packaging, or testing of the finished dosage form or new drug substance are in compliance with cGMP and application commitments. This determination may be made by conducting preapproval inspections. Method validations, method verifications, and forensic analyses will be performed to confirm the authenticity of the preapproval product and to ensure that it can be accurately assayed with the proposed regulatory methods. Postapproval inspections will monitor and enforce what is submitted in an application. "Application" means NDA, ANDA, Antibiotic Drug Application, or Abbreviated Antibiotic Drug Application and their supplements. CDER will request inspections in accordance with preestablished criteria. Optional preapproval inspections may be requested where circumstances warrant. The scope of preapproval inspections, compared with the responsibilities assigned to CDER scientists, is set forth below:

- Biobatch manufacturing: Inspection to determine the establishment's compliance with cGMP requirements, including a data audit of the specific batches on which the application is based (e.g., pivotal clinical, bioavailability, bioequivalence, and stability) is a field office responsibility. CDER scientists are responsible for the review and evaluation of the records and data submitted in the application, including the components, composition, batch instructions, in-process and finished product test points, and

specifications established for the resulting drug product.

- Manufacture of drug substance or substances: Inspection to determine cGMP compliance of the establishment is a Field responsibility. CDER chemists are responsible for the scientific review and evaluation of the records and data associated with the manufacture of the active drug substance submitted in the application or of a properly referenced Type II Drug Master File (DMF). The review will include starting materials, key intermediates, reagents, and solvents. CDER reviewers are also responsible for the review of process validation required for the manufacturing of biotechnological and certain natural substances.
- Excipients manufacture: The manufacture of novel excipients may be provided in an application or supporting DMF. Typically these excipients are noncompendial and are used in specialized dosage forms and drug delivery systems. CDER chemists are responsible for the scientific reviews and evaluation of the records and data associated with the manufacture of these novel excipients. The review will include starting materials, key intermediates, reagents, and solvents. cGMP inspections by the Field usually will be performed on request from CDER.
- Raw materials (cGMP controls): Inspection of the establishment for the drug substance and review of data on raw materials to determine compliance with cGMP requirements is a Field responsibility.
- Raw materials (tests, methods and specifications): Audit of the data submitted for CDER review in the application is a Field responsibility. CDER chemists are responsible for the scientific review of the associated data, evaluations of the adequacy of the submitted data, and ultimate approval of the tests, methods, and specifications established for the raw materials in the application.
- Composition and formulation of finished dosage form: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER reviewers are responsible for the scientific review of the composition and formulation to determine, qualitatively and quantitatively, the acceptability of the information submitted in the application.
- Container/closure system or systems: CDER is responsible for the scientific review of the container/closure system or systems to be used to package the drug product as indicated in the application. The Field may audit this data.
- Labeling and packaging controls: Inspection to determine the establishment's compliance with cGMP requirements and audit of the data submitted for CDER review in the application are Field responsibilities.
- Labeling and packaging materials: CDER reviewers are responsible for the scientific review of the labeling and packaging components associated with the drug product.
- Laboratory support of methods validation: On CDER request, Field laboratory analysts will conduct laboratory validation of the analytical methods proposed by the applicant. CDER laboratories may participate in certain instances abbreviated antibiotic drug application ([AADA] validations, etc.). CDER chemists are responsible for the review and acceptance/rejection of the analytical methods based on the laboratory results and the established specifications. Contacts between field laboratory analysts and the applicant will include the CDER chemist.
- Product (cGMP) controls: Inspection of the establishment to determine compliance with cGMP requirements, and review and audit of the data furnished to CDER in the application, are Field responsibilities. CDER scientists will request information on sterile processes, for example, laboratory controls for environmental monitoring, sterile fill operations, and evaluation and reduction of microbial contamination, to be submitted to the application for CDER review.
- Product tests, methods and specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER is responsible for the scientific review of the associated data and for the ultimate approval of the tests, methods, and specifications established for the drug product in the application. The Field will advise the center when it finds a questionable specification.
- Product stability: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data furnished to CDER in the application is a Field responsibility. This requirement applies to both the relevant preapproval batches, as discussed above, and the proposed commercial batches. CDER application review chemists are responsible for review of the proposed drug product stability protocol, specifications, and evaluation of the data submitted in support of the expira-

tion dating period proposed for the drug product in the application.

- Comparison of the relevant preapproval batch or batches and proposed commercial production batches: CDER chemists are responsible for the comparison of the formulation, manufacturing instructions, and associated in-process and finished product tests and specifications established for the relevant preapproval batch or batches with the proposed commercial production batch to determine the acceptability of the firm's proposed scale-up procedure. The Field will compare the process used to make the preapproval batches with the actual process used to manufacture the validation batches. Significant differences in these processes will be evaluated by CDER's Office of Compliance, to determine whether the differences constitute fraud, and by the reviewing officers, to determine whether differences in the processes will affect the safety and effectiveness of the resulting product.
- Facilities, personnel, equipment qualification: Review of the information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Equipment specification or specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER scientists are responsible for the review of equipment specifications furnished to the center in the application.
- Packaging and labeling (cGMP controls): Review of the controls information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Process validation: Inspection of the establishment to determine compliance with cGMP requirements and adherence to application requirements is a Field responsibility. CDER may request data to support validation of sterile processing operations; for example, environmental monitoring, equipment validation, sterile fill validation, and associated sterile operations.
- Reprocessing: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data submitted to the center in the application is a Field responsibility. CDER application review chemists are responsible for review of reprocessing protocols proposed in the application. All reprocessing procedures must be validated, or scientific data must be available to justify the reprocessing procedure. The field will audit the validation of these procedures.
- Ancillary facilities: Ancillary facilities (contract testing laboratories and contract packagers and labelers) will be inspected to determine compliance with cGMP requirements at the discretion of CDER. The name, address, and function of each ancillary facility will be indicated in the drug application, and CDER will review biological and immunological test methods and results submitted. These facilities shall also provide a certification in the drug application regarding compliance with the conditions of approval of the application.

C. Triggering of Inspections

There are two types of events that trigger inspection: categories that will regularly prompt an inspection request, and categories in which the district office may elect to perform an inspection at their discretion for elements of applications — filed or otherwise.

The following categories will regularly prompt a preapproval or cGMP:

1. New molecular entities (includes finished drug product and the active pharmaceutical ingredient)
2. Priority NDAs
3. First application filed by an applicant
4. For-Cause inspection
5. For original applications, if the current cGMP status is unacceptable or greater than 2 years
6. For certain preapproval supplements, such as site change or major construction, if the cGMP status is unacceptable
7. Treatment IND inspections (information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients)

D. Inspections/Audits

1. Manufacturing Process

i. Drug Product (Dosage Form)

In many cases, clinical production or trial runs of a new drug are produced in facilities other than the ones used for full-scale production. The facilities and controls used for the manufacture of the batch or batches are audited. For a generic drug product, the biobatch or biobatches are required to be manufactured in production facilities, using production equipment, by production personnel, and the facility is to be in conformance with cGMPs. Accurate documentation is essential so that the production process

can be defined and related to the batch or batches used for the early clinical, bioavailability, or bioequivalence studies of new drug or generic drug products. Generic product biobatches are ANDA batches that are compared to the originator/reference product to establish their equivalence. NDA biobatches are NDA batches comparing the product planned for marketing with that studied during clinical trials to establish their equivalence. The batch records submitted in the application must be audited as part of the inspection to ensure that the proposed production process is the process that was used for the manufacture of the bio/stability batches. Some manufacturers have historically made small batches that were used for biostudies and stability studies and misrepresented them as larger batches in submissions. Documentation sometimes has included research and development notebooks or batch records. Inventory records or receiving records of drug substances have been found to be of value in documenting the accountability of drug substances used in the early batches.

ii. Drug Substance (Bulk Drug Chemical)

The *Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing* (http://www.fda.gov/ora/inspect_ref/orgs/bulk.htm) and Compliance Program 7356.002F (http://www.fda.gov/cder/dmpq/compliance_guide.htm) covering Bulk Pharmaceutical Chemicals provide details of inspections covering bulk drug chemical manufacturing processes.

2. Reprocessing

The GMP regulations require reprocessing procedures to be written, and it is customary but not required that NDAs/ANDAs contain procedures covering foreseeable deviations from physical specifications (e.g., color, capped tablets, deviations from hardness specifications, etc.). If the NDA/ANDA contains a reprocess provision, the applicant must produce scientific data to establish that the procedure will result in a product that is equivalent to the original product.

3. Laboratory

Laboratory equipment and procedures must be qualified and validated. Every NDA/ANDA inspection will include both an evaluation of laboratory controls and procedures and an audit of some of the raw data used to generate results. These data may be located in research and development test logs. The authenticity and accuracy of data used in the development of a test method should be established. (See the *Guide to Inspection of Pharmaceutical Quality Control Laboratories*, July 1993.)

4. Components

The supplier and source of the active drug substance used in the manufacturing of the biobatch or clinical batch should be identified. When the manufacturer changes suppliers of drug substance from that supplier used for the manufacture of the biobatch or clinical batches, then the application should include data demonstrating that the dosage forms produced from the drug substances from the two different suppliers are equivalent in terms of conformance with established specifications, including those stated in the application. The data used to determine the adequacy of the physical specifications established for the subsequent suppliers or suppliers of the drug substance should be established.

5. Building and Facilities

The addition of any new drug to a production environment must be carefully evaluated as to its effect on other products already under production and as to changes that will be necessary to make to the building and facility. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their effect on the overall compliance with GMP requirements. For example, new products, such as cephalosporins, would require that the firm demonstrate through appropriate separation and controls that cross-contamination can not occur with regard to other products being made in the same facility. In addition, facilities that may already be operating at full capacity may not have adequate space for additional products.

6. Equipment

New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

7. Packaging and Labeling Controls

Packaging and labeling control procedures must be adequately written. Poor label control and accountability for other products may have an adverse effect on the firm's ability to ensure that the new drug will always be properly labeled. The label and packaging controls should take into account considerations of past label mix-ups and recalls.

II. REGULATORY/ADMINISTRATIVE STRATEGY

A. General

The plant should be in substantial compliance with GMP regulations and should have the necessary facilities and equipment in place to manufacture the specific product in the pending application. Some significant problems include, but are not limited to

- Application misrepresents data or conditions relating to preapproval batches; there are other inconsistencies or discrepancies raising significant questions about the validity of records
- Preapproval batches are not made in accordance with GMPs
- There is a failure to report adverse findings or test data without adequate justification: If applications are withheld because of significant cGMP noncompliance, and the GMP deficiencies also apply to commercially marketed products, then action must be taken to ensure that the deficiencies are corrected

B. Process Validation

Approvals are not generally withheld on the basis of a lack of complete, full-scale, multiple-batch process validation. Although the agency does not require the manufacturer to fully validate the manufacturing process and control procedures of the commercial batch production before approval, the CDER will require that certain data be filed to demonstrate that a plant's sterilization and aseptic fill process has been qualified. These filing issues are under the control of the CDER's reviewing divisions. Because complete process validation is not required before approval, it is not required to audit complete process validation for sterile and nonsterile processes until the application has been approved. However, if the plant has already validated the process before the preapproval inspection, the validation is evaluated during the preapproval inspection. The inspection team lists deficiencies in the validation process on the FDA-483 and advises the plant official that complete validation must be completed before shipment. Applicants and sponsors must be able to justify filed specifications with scientific data. In other words, the sponsor should have conducted sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data form the basis for the review and evaluation of the application, and these specifications form the basis of the validation protocol that may be developed following the approval of the application. The final step in the product development process is validation that the process will perform consistently. Companies are expected to validate the process using the specifications listed in the filing. Process validation requirements for the manufacture of bulk pharmaceutical chemicals (BPCs) differ somewhat from those involving dosage forms. The *Guide to Inspection of BPCs* issued in 1991 states that BPC manufacturers are expected to adequately determine and document that significant manufacturing processes perform consistently. The type of BPC, the range of specifications, and other factors determine the extent of the process development and documentation required. The documentation system required for early process steps must provide a chain of documentation, and although it need not be as comprehensive as in the later parts of the process, the manufacturer is required to identify and control the key steps in the process. Though many BPC manufacturers have recently initiated validation programs, not all BPCs can be validated simultaneously. Therefore, the inspections do not recommend taking any legal action where a firm has an adequate program in place, including reasonable milestones. Regulatory actions are recommended where there is a lack of validation and where there is evidence of a significant number of failed batches.

C. Key Elements

The key elements of an inspection are to ensure that the facility is capable of fulfilling the application commitments to manufacture, process, control, package, and label a drug product following GMP; the adequacy and accuracy of analytical methods submitted, to ensure that these methods are proper for the testing proposed; correlation between the manufacturing process for clinical trial material, bioavailability study material, and stability studies and submitted process; that the scientific data support full-scale production procedures and controls; that only factual data have been submitted; and that the protocols are in place to validate the manufacturing process.

The CDER, which governs the preapproval inspections, can additionally require preapproval inspections in the case of drugs with narrow therapeutic range, where new chemical entities are involved, where drugs are difficult to manufacture, in the case of drugs that represent a new dosage form for the application, where it is the first approval for the company, in the case of a poor GMP track record, and where generic versions of one of the 200 most prescribed drugs is involved (see Table 4.1).

D. Strategies for Preinspection

Preinspection preparation involves developing both short-term and long-term strategies. The short-term strategy may comprise

- Determining the state of cGMP compliance of all of the manufacturing and development facilities listed in the NDA for the product under review: This should be carried out by the quality assurance division of the firm.
- Compiling all relevant regulatory documents for use by the FDA inspectors at the potential inspection sites: This should be done by the regulatory affairs group of the firm; the efforts

TABLE 4.1
Active Pharmaceutical Ingredients from the Top 200 Prescription Drugs in 2002

Acetaminophen+Codeine
Acyclovir
Albuterol
Alendronate
Allopurinol
Alprazolam
Amitriptyline
Amlodipine
Amlodipine/Benazepril
Amoxicillin
Amoxicillin+Clavulanate
Amphetamine Mixed Salts
Aspirin
Atenolol
Atorvastatin
Azithromycin
Benazepril
Bisoprolol+Hydrochlorothiazide
Budesonide
Bupropion hydrochloride
Buspirone
Captopril
Carbidopa+Levodopa
Carisoprodol
Carvedilol
Cefprozil
Celecoxib
Cephalexin
Cetirizine
Ciprofloxacin
Citalopram
Clarithromycin
Clindamycin
Clonazepam
Clonidine
Clopidogrel
Conjugated Estrogens+Medroxyprogesterone
Conjugated Estrogens
Cyclobenzaprine
Desloratadine
Desogestrel+Ethinyl Estradiol
Diazepam
Diclofenac
Digoxin
Diltiazem
Divalproex
Doxazosin
Doxycycline
Enalapril
Esomeprazole
Estradiol
Ethinyl Estradiol+Norethindrone
Famotidine
Fenofibrate
Fexofenadine
Fexofenadine+Pseudoephedrine
Fluconazole
Fluoxetine
Fluticasone
Folic Acid
Fosinopril
Furosemide
Gabapentin
Gemfibrozil
Glimepiride
Glipizide
Glyburide
Glyburide+Metformin
Human Insulin 70/30
Human Insulin NPH
Hydrochlorothiazide
Hydrocodone+APAP
Hydroxyzine
Ibuprofen
Insulin Lispro
Ipratropium+Albuterol
Irbesartan
Isosorbide Mononitrate S.A.
Lansoprazole
Latanoprost
Levofloxacin
Levonorgestrel+Ethinyl Estradiol
Levothyroxine
Lisinopril
Lisinopril+HCTZ
Loratadine
Loratidine+Pseudoephedrine
Lorazepam
Losartan
Losartan+Hydrochlorothiazide
Meclizine
Medroxyprogesterone
Metaxalone
Metformin
Methylphenidate Extended Release
Methylprednisolone
Metoclopramide
Metoprolol
Metronidazole
Minocycline
Mirtazapine
Mometasone
Montelukast
Mupirocin
Naproxen
Nifedipine
Nitrofurantoin
Norethindrone+Ethinyl Estradiol
Norgestimate+Ethinyl Estradiol
Nortriptyline
Nystatin
Olanzapine
Omeprazole
Oxybutynin
Oxycodone
Oxycodone+APAP
Pantoprazole
Paroxetine
Penicillin VK
Phenytoin
Pioglitazone
Potassium Chloride
Pravastatin
Prednisone
Promethazine
Promethazine+Codeine
Propoxyphene N+APAP
Propranolol
Quetiapine
Quinapril
Rabeprazole
Raloxifene
Ramipril
Ranitidine
Risedronate
Risperidone
Rofecoxib
Rosiglitazone maleate
Salmeterol
Salmeterol+Fluticasone
Sertraline
Sildenafil Citrate
Simvastatin
Spironolactone
Sumatriptan
Tamoxifen
Tamsulosin
Temazepam
Terazosin
Tetracycline
Timolol Maleate
Tolterodine
Topiramate
Tramadol
Tramadol+Acetaminophen
Trazodone
Triamcinolone
Triamterene+HCTZ
Trimethoprim+Sulfamethoxazole
Valacyclovir
Valdecoxib
Valsartan
Valsartan+HCTZ
Venlafaxine
Verapamil
Warfarin
Zolpidem

also include a summary of the commitments made to the FDA.
- Identification of key batch records: These documents are then compared with the commitments that are contained in the Regulatory Commitment Document (see above). Any discrepancies identified are resolved, and explanations are documented when appropriate. This is done by the product development group in collaboration with the quality control and regulatory affairs departments.
- The history of analytical methods used to control the product is prepared: The analytical development department prepares a chronological history of the various analytical methods used during the product development. This includes justifications for any changes made in the methods during the development process and a comparison of the methods used to release clinical batch vis-à-vis the commercial batches.
- Transfer of analytical methods to the site or sites where they are used: This is the responsibility of the analytical development division. Raw data supporting a successful transfer should be readily available to the inspectors.
- Scale-up ensuring that installation qualification, operational qualification, performance qualification (IQ/OQ/PQ) activities are properly conducted: These include cleaning validation, process validation, sterilization validation, and so forth, according to established corporate procedures.
- The development report has two main sections, one that addresses the dosage form and one that deals with the bulk drug substance: The product development scientist compiles the experimental evidence to demonstrate bioequivalency for the first clinical trial lot through those lots that will be used for launch. The report further includes a description of the current process along with a description of the chemical/physical characteristics, purity, related substances, specifications, and stability of the drug substance.

The long-term strategy of preparing for a pre-NDA approval inspection generally comprises

- Incorporating drug development process in the preparation to allow the FDA to review the documents from the earliest stages of development
- Establishing measures of cGMP for the production and distribution of clinical trial material; this may be different from the commercial production systems and addresses the issues of stability guidelines developed by the analytical laboratory in consultation with the quality assurance, the policy on the management of deviations (fully justified), batch disposition of clinical trial lots, change documentation — which is another critically important part of a quality system for product development, process validation, training, management notification—which sets the standard for notification of corporate research management in the event that a quality issue occurs with clinical trial materials.

E. International Inspection

The FDA inspections are conducted in the same manner for both domestic and international firms, but in practice there are legal and logistic reasons for the FDA to follow different procedures when scheduling and conducting international inspections for the purpose of verifying integrity of information submitted and ascertaining compliance with the cGMP regulations. There are four differences between domestic and international inspections: international inspections are nearly always scheduled in advance, language barriers pose unique challenges during international inspections, international inspections are typically of shorter duration than domestic inspections that are conducted for the same purpose, and international firms are reinspected less often than are domestic facilities.

When inspecting domestic firms, the FDA has the responsibility over all products manufactured, and thus inspections are often extended to include other products as well. At foreign facilities, the FDA generally has interest only in products that will be marketed in the United States, and it is likely that the firm inspected may only be marketing a handful of products in the United States, though it may have a large presence. In addition, most international inspections are completed within a fixed duration, as the inspection may be heading for similar audits in the region elsewhere and it is not often possible to make last-minute changes to itinerary. In domestic audits, the inspectors routinely interrupt the audit and return later to complete it; such is not the case with the foreign inspections.

Unless a firm has previous experience with such audits, it is highly recommended that the firm assign responsibilities for PAI readiness, determine the PAI schedule, anticipate FDA needs, verify application integrity, and verify GMP compliance on their own before the visit.

Whereas the regulatory submissions must be in English, the FDA expects that raw data and original records may be in the native language, and this is acceptable: there is no need to translate documents that are

created in the native language. In fact, it is ill-advised to convert documents, as this may result in errors that can unnecessarily create confusion in the inspection. However, the summary documents as requested by the FDA may be translated before the arrival of inspectors. Where attachments were included in the regulatory submissions, these should be available with proper certification for their authenticity.

Foreign inspections almost always follow a preset routine, despite individual style, which depends on the qualification of the inspector (whether he or she is a microbiologist or a chemist, for example).

Summary documents are critical to a successful start of the audit; the FDA would rely heavily on the development reports, particularly as they pertain to early development phases of development, scale-up, and the development of analytical methods. Information contained in the development report is also useful for the firm's management to present overviews to the FDA about key development activities at the start of an inspection. Well-written, comprehensive reports may be sufficient for the purpose of the inspection without the FDA getting into inquiry about the raw data. Because the FDA is short of time in foreign inspections, they are more likely to accept the report in lieu of a larger number of support documents; as a result, the importance of a well-written, comprehensive development report is the most important tool for foreign firms. A lack of reports or incomplete reports will almost always cause the FDA inspectors to inquire about the raw data — something that should be avoided, if at all possible. Raw data always spells trouble in every inspection. An unnoticed peak in the active pharmaceutical ingredient (API) thin layer chromatography (TLC), a missing signature, numbers changed without crossing it out, and so forth, are some of the common occurrences that raise flags as the audit gets deeper.

Next to the preparation of the development report, the most important thing for the foreign firm to do is to "break ice" with the FDA inspectors. Almost always there are cultural and etiquette differences that must be overcome immediately. Although there is no need for an elaborate protocol, the firm is expected to inform the FDA inspectors about the matters indigenous to the region, such as traffic problems, hotel accommodation, food availability, and most important, any local customs that may adduce a behavior with which the inspectors may not be familiar. It is also a good idea to start the meeting with the inspectors by expressing a desire to be apprised of any findings as they occur, as it is easier to rebut or explain the situation at that moment. These situations often arise as a result of different systems of document keeping, document routing, and personnel management.

Where deficiencies are found, the firm should attempt to rectify them during the visit while keeping the FDA inspectors informed of the changes made to overcome the objections. Know that the FDA personnel are expected to report corrective actions in the Environmental Impact Report (EIR). When it is not possible to complete the corrective actions before the FDA leaves the premises, it is in the firm's best interest to report steps that have already been taken toward initiating a corrective action plan. In addition, the FDA is concerned about the steps taken to prevent recurrence of such problems and the evaluations made to determine whether the objectionable conditions may apply to other areas of the facility, as well as the steps taken by the company to determine the cause of specific objections found by the FDA. Also, falsification of documentation that a corrective action has been taken when it may not have been can land the firms in deep trouble in the follow-up inspections. The FDA becomes suspicious when the firm provides evasive or inconsistent answers, shows unexpected body language or behavior in responding, or an inconsistent response is received from different employees. It is important, therefore, that the firm go through a mock-up exercise involving all those employees who may eventually end up talking to the FDA inspectors.

At the end of inspection, the FDA conducts an exit discussion with management to deliberate on the inspection findings. Should there be any GMP-related deviations or other objectionable conditions, they will leave with the company a written list of observations (FDA-483) and will provide management with the opportunity to discuss the FDA findings. The purpose of the FDA-483 is to list objectionable conditions and practices found by the FDA investigator; it is not intended to report any favorable or acceptable conditions that may have been observed during the inspection. Each of the FDA-483s issued is subjected to further review by FDA management in the field offices or at headquarters units to determine the validity and significance of each item. It is imperative that personnel completely understand the reason or reasons that the FDA considers a condition or practice to be objectionable before the inspection team departs. As mentioned earlier, it is in the best interest of the FDA as well that issues are closed before their departure, as the inspectors may not be able to return soon, and it will create a substantial burden on the firm if the approval is withheld; this is a significant benefit in international inspections of which the firms should take full advantage.

Management should verbally respond to the inspection findings during the discussion of the FDA-483. Each item should be discussed individually, and the company personnel should provide additional explanations where appropriate and should state their intentions for items where they have made or intend to make improvements. When companies have initiated corrective actions, it is imperative that the FDA be informed of the actions taken (especially corrections that have already been completed). The company should request that the FDA team report in their EIR the corrections that have been accomplished. If

the FDA has had the opportunity to verify the corrections, it would be appropriate to ask them to comment on the adequacy of the actions taken by the company (i.e., Were they satisfied with the corrective actions, or should the firm consider further actions?).

To demonstrate to the FDA that corrective actions have been taken, firms should provide to the FDA team the copies of documents that show corrections such as revised standard operating procedures (SOPs), change control records for facility improvements, training documentation, and results of analytical testing. In those situations in which the firm may need some time to decide appropriate corrective actions, it is advisable to inform the FDA team that a written response will be provided within a reasonable period (ideally within 2 weeks). It is extremely important to stick to this timeline, as it takes about 2 weeks for the inspector to file his or her EIR: It is most beneficial, strategically, to have the response of the firm be recorded in the EIR. The firm, however, should not make promises that it knows cannot be fulfilled, such as requiring substantial financial outlay that the firm may not be able to afford, or giving a timeline that is too restrictive or unrealistic. The firms should not risk creating a credibility problem in the follow-up visits. The FDA encourages an open discussion of each item listed on the FDA-483, and the FDA team should be able to defend its observations. If management believes that an item listed on the FDA-483 is incorrect or does not accurately reflect the true conditions found by the FDA investigator, this should be discussed in sufficient detail until the issue can be resolved to mutual satisfaction. If the observation is an error caused by misunderstandings, it is essential that there be full discussions to ensure that the FDA has accurate and complete information. This is why it was earlier recommended that the firm develop an open communication with the FDA, finding out the deviations as they are discovered rather than in the end-of-visit reporting. If the FDA has all of the relevant information and facts, but the FDA team has reached the conclusion that the firm's practices or conditions are unacceptable, then the FDA-483 observation will remain. The FDA does routinely alter its FDA-483; however, where disputes remain on how the FDA has interpreted a finding vis-à-vis the position firm takes, it is important to identify which data were used by the FDA that formed the basis of their decision; these data should then be verified, and if it is discovered that discrepancies occurred that were unintentional, the FDA inspectors should be informed as soon as possible after they leave the firm's premises.

When the FDA team has not found objectionable conditions, they will terminate the inspection (an FDA-483 will not be issued). In such cases, the company will not receive anything in writing from the FDA team. The firm, however, reserves the right to request the FDA to issue a statement to this effect and to ask for an exit discussion. However, one should be extremely careful about engaging the FDA inspectors in discussions that are superfluous, to prevent any inadvertent disclosure that might change their opinion about the inspection.

The Application Integrity Policy (AIP) is a formal administrative program that the FDA uses to deal with fraud, scientific misconduct, or other instances in which wrongful acts have been committed or are suspected. The AIP, introduced in 1990 as consequence of the generic drug scandal, was formerly called the "fraud policy." The AIP is invoked when the integrity of data or information in applications filed with the FDA has been compromised or questioned. Examples of actions that may prompt investigations include submission of false or fraudulent data, making untrue statements to the FDA officials, offering illegal gratuities, and other actions that subvert the integrity of an application. The primary enforcement options that are available to the FDA under the AIP program include withholding of approvals, product recalls, and civil and criminal penalties. However, note that the FDA may not have a legal jurisdiction over a foreign establishment, and thus the penalties are mainly the rejection of application and banning the firm from submitting future applications.

F. Product Stability Data

One of the most widely cited observations in the FDA audits is the lack of or inadequate data to support the stability of the product. This applies to domestic as well as international audits, though more problems arise in international audits, where the firm may have used a different climatic zone for testing the product. A robust stability program includes study of loss of active ingredient (potency), increase in concentration of active ingredient, alteration of bioavailability, loss of content uniformity, decline in microbiological status, increase in possibly toxic decomposition product, loss of pharmaceutical elegance, and modification in any other factor of functional relevance (e.g., loss of adhesion strength in a transdermal).

The stability data that should available at the time of preapproval inspection include

- Adequate test method: The assays of the active component should be stability-indicating; that is, they can be separated from the degradation products and other components of the formulation. Furthermore, the degradation products should be quantitated and all methods should be validated not only at the beginning of the testing but also through the testing period.
- Characterization of drug substance: Where a reference standard is used in an ANDA, this aspect is set aside. However, where a new chemical entity (NCE) is involved, a large vol-

ume of data would generally be required to establish the degradation profile of the new drug, especially if this happens to be a macromolecule; when the testing requires evaluation by a biological response, the difficulties in validating the test method rise exponentially. Where an entirely new stability-indicating assay is established, it is necessary to demonstrate that the procedure is indeed stability-indicating by forced degradation studies. For protein drugs, incomplete knowledge of the molecule makes it difficult to demonstrate the stability-indicating nature of the assay.

- Calibration of equipment: This is a routine requirement, and the FDA inspectors may not review these data if they find that the firm is in general good compliance with the cGMP. However, these data should be updated and current at all times.
- Assay validation parameters: The common parameters that require attention include accuracy, limit of detection, limit of quantification, linearity, precision, range, recovery, robustness, sample stability (on storage and during assay), specificity and selectivity, and systems suitability. Two additional parameters that may need special attention are transferability and comparability. This applies to both chemical and physical testing where used. Because stability-indicating methods evolve over time, revalidation is critical. Partial revalidation is required whenever significant changes are made either in the method itself or in the material analyzed, which could reasonably be expected to affect the results obtained (e.g., changes in equipment or suppliers of critical supplies).
- Preformulation studies (bulk drug substance): Stability data of the bulk drug substance alone or in model test systems is required, and most companies find this to be weakest point of their presentation to the FDA.
- SOPs: During the PAI, the FDA investigators routinely examine the SOPs that relate to the development and operation of the stability program to ascertain the strengths and weaknesses of the program, as well as ensuring compliance with the SOPs. Firms should understand that there are no official guidelines on how to write an SOP, what methods to use, and who should be responsible for doing it. What the FDA looks for is that, given an approved SOP, the firm adheres to its own guidance. Should doubts arise that the firm is not following its own guidelines, suspicion grows about the firm's overall ability to comply with the cGMP regulations.
- Room temperature and accelerated test data: For products that will be labeled to require storage at controlled room temperature, long-term studies at 25˚C ± 2˚C with 60% relative humidity (RH; ± 5%) with at least 12 months of data are needed. Accelerated studies at 40˚C ± 2˚C and 75% ± 5% RH with at least 6 months of data are also normally required. However, the ICH does allow for a less rigorous accelerated test if the 40˚C test cannot be passed. When "significant change" occurs during the 40˚C accelerated study, an intermediate test, such as 30˚C ± 2˚C and 60% RH ± 5% for 12 months, can be used. Significant change is defined as a 5% loss of potency, exceeding pH limits, dissolution failure, and failures of physical specifications (hardness, color, etc.). If products are to be labeled with instructions for storage at a temperature of less than 25˚C, then the accelerated studies can be performed at a temperature less than 40˚C; however, the conditions should be at least 15˚C above those used for long-term evaluation. Products for which water loss may be more important, such as liquids or semisolids in plastic containers, it can be appropriate to replace high-RH conditions by lower RH, such as 10% to 20%. If, during clinical trials, a number of different formulations have been used that differ in either formulation or processing variables from the product intended for the market, it may be appropriate to "build bridges" between the various formulations if there is reason to believe that the changes in the formulation or processing variables are such that might reasonably be expected to significantly modify stability. The FDA SUPAC (scale-up and postapproval changes) Guideline should be consulted about the importance of such changes.
- Contract laboratory stability testing: Where contract work is involved, complete details about the facility conducting the testing should be available. The FDA may choose to visit that facility as well, unless it is an approved facility that has undergone several FDA inspections in the past.

Developing stability data for an ANDA product generally requires fewer laboratory studies than those required with an NCE. The primary goal of an ANDA should be to mimic the stability profile of the innovator product, barring any intellectual property issues that might prevent the generic manufacturer from formulating a sim-

ilar product. (Of course, there is nothing to prevent an ANDA sponsor from trying to formulate a product with a longer shelf life than that of the innovator, and this idea has been considered by some companies.) The formulation of generic products requires developing a source of API — a DMF source — that is substantially identical in its stability profile to the innovator API; where reference standards are not yet available, this may create serious problems. In addition, it is often difficult to obtain impurities in sufficient quantity to validate the test methods. As a result, much effort is needed in making this part of the stability profile appear as comprehensive as possible. Firms often use bracketing, or matrixing — a form of partial factorial experimental design — to reduce their experimental load, and it is well accepted; however, before adopting this method, the firm is advised to consult with the FDA, as the power of test required may change with the type of API involved. Also, normalization of stability results is not usually desirable, and the plots of percentage of label claim as a function of time should not be normalized so that all batches originate at 100% of label claim. In considering batch-to-batch variability in three or more batches, the FDA is interested in both intercepts and slopes. The arguments often adduced by European companies that the slope is more important in establishing shelf life are not acceptable to the FDA. The FDA also considers delay in testing of samples a serious issue in the stability profiling in addition to the calibration and validation of the stability chambers. Know that the FDA takes a hard-line approach when it comes to the conduct of stability testing. Firms often are greatly surprised by how important the FDA considers these "nuts and bolts" issues, such as crowded stability chambers with poor air circulation, lack of proper calibration, and evidence that the temperature fluctuation is not more than 2°C.

G. Validation of Processes

Next to the problems frequently recorded in stability profiles of drug products is the lack of or inadequacy of the documents that affirm that the process used for the manufacture of a biobatch of the commercial batch was fully validated. Validation is a requirement of both the development stage and the final batches. Process validation is defined as establishing documented evidence, which provides a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. To provide the FDA with sufficient documentation, firms should prepare a flow diagram of the process in a logical flow, identifying various unit operations. Firms are required to perform validation of three formal batches.

The general principles of process validation involve prospective process validation (also called premarket validation), retrospective process validation, revalidation, and concurrent process validation. Prospective process validation is the most important for an FDA pre-NDA approval inspection of a NCE or API in a dosage form or delivery system.

Prospective validation is conducted before the distribution of either a new product or an existing product made under a revised manufacturing process where such revisions may affect product specifications or quality characteristics (attributes). This involves documenting critical step analysis, in which the unit operations are challenged during the process qualification stage to determine, using either "worst case" analysis or a fractional factorial design, critical process variables that may affect overall process performance. During formal, three-batch, prospective validation, critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should fall well within finished product specifications.

Retrospective validation involves using the accumulated in-process production and final product testing and control (numerical) data to establish that the product and its manufacturing process are in a state of control. Valid in-process results should be consistent with the drug products' final specifications and should be derived from previous acceptable process average and process variability estimates, where possible, and determined by the application of suitable statistical procedures, that is, quality control charting, where appropriate. The retrospective validation option is selected when manufacturing processes for established products are considered to be stable and when, on the basis of economic considerations and resource limitations, prospective qualification and validation experimentation cannot be justified.

Before undertaking either prospective or retrospective validation, the facilities, equipment, and subsystems used in connection with the manufacturing process must be qualified in conformance with cGMP requirements.

Concurrent validation is conducted under a protocol during the course of normal production. The first three production-scale batches must be monitored as comprehensively as possible. The evaluation of the results is used in establishing the acceptance criteria and specifications of subsequent in-process control and final product testing. Some form of concurrent validation, using statistical process control techniques (quality control charting), may be used throughout the product manufacturing life cycle.

Revalidation is required to ensure that changes in process or in the process environment, whether introduced intentionally or unintentionally, do not adversely affect product specifications and quality characteristics. Firms should put a quality assurance system (change control) in place that requires revalidation whenever there are significant changes in formulation, equipment, process, and packaging that may affect product and

manufacturing process performance. Furthermore, when a change is made in a raw material supplier, the supplier of API should be apprised of the critical requirements of impurities. Revalidation is often required in following conditions:

- Change in an API or a key excipient, or primary packaging
- Change or replacement in a critical piece of equipment
- Significant change in processing conditions that are known to affect either subsequent unit operations or product quality
- Change in a location, site, or support system (e.g., utilities)
- Significant change in batch size from what was validated and that affects the operation of or selection of manufacturing equipment
- Where several batches fail sequentially

Process performance requalification studies before revalidation assignments are currently required for sterile products only; some of these issues can be covered in the yearly filings. However, firms are urged to review the most current SUPAC guidelines for the specific type of product manufactured.

An important document that all firms must have is the validation master plan, which enables creation of an overview of the validation effort. This plan should be put together early in the drug development process and updated on a regular basis as the drug product enters various stages of development. The plan is basically a layout of how the various activities will be performed against a predetermined time line (perhaps using Gantt or Program Evaluation and Review Technique [PERT] chart format). Of significance are the critical paths in the plan and how they are linked to objective achievement.

The validation program generally follows the following order:

- Selection of raw materials and components
- IQ/OQ of facilities, equipment, and systems
- Performance and process qualification stages
- Protocol-driven, three-batch, formal process validation

Running these in series and in parallel, much time can be conserved. The three stages with respect to equipment qualification are sometimes referred to as Equipment Validation, comprising IQ, which ensures that a piece of equipment has been correctly calibrated and installed in accordance with the equipment manufacturer's recommendations (proper voltage, amperage, clearance from wall, exhaust requirements, etc.). It is important to understand that IQ is also required for all utility systems. In most instances, once the installation is complete, IQ cannot be performed retroactively, such as in the case of heating, ventilation, and air-conditioning or water systems; the FDA considers this phase of planning crucial in evaluating the readiness for compliance with GMP regulations. The next phase is OQ, comprising procedures and documentation that show that the facility, support system, or piece of equipment performed as intended throughout all anticipated operating ranges under a suitable load. In this phase the systems or equipment are challenged to the limits of operation. The final phase is PQ, which demonstrates that the facility, support system, or piece of equipment performed according to a predefined protocol and achieved process reproducibility and product acceptability.

Given below is a proposed outline for a prototype validation protocol:

1. Purpose of the entire validation and prerequisites
2. Description of the entire process and subprocesses, including flow diagram and critical step analysis
3. Validation protocol approvals
4. IQ and OQ, including blueprints or drawings
5. Qualification report or reports for each subprocess
   a. Purpose
   b. Methods/procedures
   c. Sampling and testing procedures, release criteria; for example, reporting function
   d. Calibration of test equipment used; for example, test data
   e. Summary of results
   f. Approval and requalification procedure
6. Product qualification, test data from prevalidation batches
7. Product validation, test data from three formal validation batches
8. Evaluation and recommendations (including revalidation/requalification requirements)
9. Certification (approval)
10. Summary report with conclusions

The validation protocol and report may also include the product stability data or a summary and documentation concerning cleaning and analytical validation.

The pilot-production program is generally a result of cooperation between the development laboratories and the manufacturing department. Technology transfer documentation applies to processes as well as to the systems being qualified and validated and their testing standards and testing methods. This documentation is important, particularly where an NDA is involved.

The concept of validation should be incorporated during every phase of product and process development:

1. Preformulation studies incorporate API qualification and evaluation of key excipients. Studies should incorporate studies of combinations of API and excipients and a rationale developed for the levels of various excipients chosen. Interactions between the API and excipients are expected and should not form the basis of altering the choice so long as data can be collected to show that the API is available through the shelf-life.
2. Once a selection of ingredients is made, the work is transferred to the formulation laboratory to establish preliminary product design as well as prototype formulations. If the product manufactured at this level is to be used in humans, the manufacturing should be done at a GMP level.
3. Once a laboratory batch (often called 1×) has been determined to be both physically and chemically stable based on accelerated, elevated-temperature testing (i.e., 1 month at 45˚C or 3 months at 40˚C or 40˚C/80% RH), the next step is to scale the product and its process to a (10×) pilot-laboratory-size batch or batches. The pilot-laboratory-size batch represents the first replicated scale-up of the designated formula. The size of the pilot-laboratory batch will usually range between 10 and 100 kg, 10 and 100 L, or 10,000 and 100,000 U. These pilot-laboratory batches are often used in clinical trials and bioequivalency studies. According to the FDA, the minimum requirement for a biobatch is 100,000 U. The pilot-laboratory batches are usually prepared in small pilot equipment within a designated cGMP-ready facility. Process-development (process-qualification) or process-capability studies are normally started in this important stage of the scale-up sequence. To evaluate the critical control parameters and their unit operation, constraint analysis techniques followed by fractional factorial designs are often used to challenge the tentative control limits (so-called "worst-case analysis") established for the process at this intermediate stage.
4. A pilot production is at about a 100× level; in general, the full scale-batch and the technology transfer at this stage should comprise preformulation information, product development report, and product stability and analytical methods reports. This is the time to finalize the batch production documentation for the 100× level. The objectives of prevalidation trials at this stage are to qualify and optimize the process in full-scale production equipment and facilities. These studies should not be rushed, as they are followed by a formal validation cycle, and rushing the prevalidation protocols may result in costly errors later on.
5. The formal validation is often completed after the PAI, where three-batch process validation will be conducted in accordance with the protocol approved during the preapproval inspection. The primary objective of the formal process validation exercise is to establish process reproducibility and consistency. Such validation must be completed before entering the market. The formal validation studies continue through packaging and labeling operations (in whole or in part), so that machinability and stability of the finished product can be established and documented in the primary container-closure system.

H. Change Control

Changes in the processes, systems, and formulations are inevitable. However, procedures for change control should be in place before, during, and after the completion of the formal validation program — to ensure that the process continues in a validated, operational state even when small noncritical adjustments and changes have been made to the process. These changes should be critically reviewed by the validation or CMC committee. The change control system allows innovation and process improvements, making it more flexible without prior formal review on the part of the NDA- and ANDA-reviewing function of the FDA. The supplemental procedures with respect to the Chemistry and Manufacturing Control sections of NDAs and ANDAs are covered through annual SUPAC review documentation procedures, with change control procedures providing assurance that process validation will remain more proinnovative.

1. Cleaning Validation

According to section 211.67 Equipment Cleaning and Maintenance of cGMP regulations, equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product. This includes materials used in clinical trials as well as the commercial drug product. Written SOPs must ensure that cleaning and maintenance of equipment in both product development laboratories and manufacturing facilities is strictly adhered to. Records should be kept of maintenance, cleaning, sanitizing, and inspection. These records are likely to be requisitioned by the FDA during the course of the preapproval inspection. The objective of cleaning validation of equipment and

utensils is to reduce the residues of one product below established limits so that the residue of the previous product does not affect the quality and safety of the subsequent product manufactured in the same equipment. Some of the equipment design considerations include type of surface to be cleaned (stainless steel, glass, plastic), use of disposables or dedicated equipment and utensils (bags, filters, etc.), use of stationary equipment (tanks, mixers, centrifuges, presses, etc.), use of special features (clean-in-place systems, steam-in-place systems), and identification of the difficult-to-clean locations on the equipment (so-called "hot spots" or critical sites). It is important to realize that the FDA has tightened significantly the cleaning validation policies, particularly if there are biological products involved; the therapeutic proteins and peptides are specifically the target of FDA inspection.

The cleaning procedures define in certain terms the amounts and the specific type of cleaning agents or solvents used, and the procedure includes complete details about what is to be cleaned and how it is to be cleaned. As always, the methods focus on the worst-case conditions, such as the higher-strength, least soluble, most difficult-to-clean formulations manufactured within the facility that may be alternated. Cleaning procedures should identify the time between processing and cleaning, cleaning sequence, equipment dismantling procedure, need for visual inspection, and provisions for documentation.

The analytical methods chosen to validate the cleaning process may include the HPLC, TLC, spectrophotometry, TOC (total organic carbon), pH, conductivity, gravimetric, and so forth. The sampling techniques chosen may include direct surface sampling, using swabs and gauze or rinsing, depending on the residue limit to be established on the basis of the sampling site, type of residue sought, and equipment configuration (critical sites vis-à-vis large surface area) consideration. The analytical and sampling methods should be challenged in terms of specificity, sensitivity, and recovery. The residue limits to validate the cleaning must be practical, achievable, and verifiable, and they must ensure safety. The potency of the selected drug and the presence of degradation products, cleaning agents, and microorganisms should be taken into consideration.

As a general rule, use these limits: not more than 10 ppm, not more than 0.001 of the dose of any product will appear in the maximum daily dose of another product, and no physical or chemical residue will be visible on the equipment after cleaning procedures have been performed.

2. Analytical Methods Validation

Nothing is more critical to a successful PAI than an elegant presentation of analytic methods validation in the eyes of the FDA investigators. Not only does this tell the investigators about the assurance provided for the correct testing of the product, but this also reflects on the overall understanding of the firm on compliance with the cGMP. Analytical methods go to the heart of a validated process for drug product manufacture. To establish what is tested and what the amounts involved are may appear a simple process at the outset, yet there remain many elaborate steps that will ensure that every time an analysis is performed, the test results can be relied on. Analytical methods that form the technical package for a product include not only the API but also inert excipients, the impurities in both, the residue from previously used materials and operations, the composition of in-process blends and compositions, and obviously the finished product before its release. To ascertain that the methods used are qualified for each of these phases of testing, a large volume of data is generally collected at all stages of product development, for scale-up and final manufacturing batches, and at all stages of validation and stability protocol development.

While validating a production process, several steps were listed as they pertained to each of the components of manufacturing: equipment, process conditions, personnel, and so forth. These key elements multiply rapidly when it comes to analytical methods validation. Take, for example, HPLC — the most commonly used method of analysis. A typical analytical method would involve use of columns, pumps, heaters, detectors, controllers, samplers, sensors, recorders, computers, reagents, standards, and operators — put together as a system. Each of these components and systems needs independent validation, followed by a validation of the system. Note that when this equipment is used to manufacture a product such a therapeutic proteins wherein HPLC techniques are used for the purification purpose, then all additional requirements of a manufacturing system also apply, including, but not limited to, the requirement that the equipment be of a sanitary kind. This limits the choice for manufacturers, and these considerations should be taken into account in the first selection of equipment.

The suitability of analytic method must be clearly demonstrated. This involves developing data on accuracy, precision, and linearity over the range of interest; that is, 80 to 120% of label potency. Data demonstrating the specificity, sensitivity, and ruggedness of the method and the limits for degradation products or impurities should be included. It is also important to study degradation products and impurities, which should be adequately identified and characterized. Data collected must demonstrate recovery of actives and lack of interference from other components, reagents, and standards. In addition, data characterizing day-to-day, laboratory-to-laboratory, analyst-to-analyst, and column-to-column variability should be developed to supplement reproducibility and ruggedness information. The validated analytical method

should be stability-indicating. Recognition by an official compendium will often simplify the requirements listed above, but it still requires a verification process. Biological assay methods as well as the identification and analysis of microorganisms should be held to similar but reasonable standards in conformance with the limitation of biological testing.

3. Computer System Validation

New to the industry is the requirement that all electronically kept records be validated in accordance with the CFR (Title 21, Volume 1, part 11 revised April 1, 2003 requirement. This is particularly true of instances in which the systems are custom-designed and, furthermore, where computer-controlled automated processes are used. There remain many misconceptions about makes up computer validation. The CFR guideline as listed below should be well understood:

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A — General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with Sec. 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

Subpart A — General Provisions

Sec. 11.2 Implementation.

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:

(1) The requirements of this part are met; and

(2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Subpart A — General Provisions

Sec. 11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms also apply to this part:

(1) Act means the Federal Food, Drug, and Cosmetic Act [secs. 201-903 (21 U.S.C. 321-393)].

(2) Agency means the Food and Drug Administration.

(3) Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

(4) Closed system means an environment in which

system access is controlled by persons who are responsible for the content of electronic records that are on the system.

(5) Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

(6) Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

(7) Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.

(8) Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.

(9) Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B — Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

(d) Limiting system access to authorized individuals.

(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Subpart B — Electronic Records

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in Sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Subpart B—Electronic Records

Sec. 11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and
(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Subpart B — Electronic Records

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C — Electronic Signatures

Sec. 11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.
(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
(1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
(2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Subpart C — Electronic Signatures

Sec. 11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:
(1) Employ at least two distinct identification components such as an identification code and password.
(i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.
(ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
(2) Be used only by their genuine owners; and
(3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.
(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Subpart C — Electronic Signatures

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.
(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.
(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.
(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

To understand fully the importance of computer validation, one must realize that computers can perform the functions humans used to. Instructions such as SOPs are needed to instruct humans as to what functions to perform

and in what order. When computers are used, these instructions are programmed. Computer systems are extensions of the processes that they are designed to control or monitor; as a result, all computer-controlled manufacturing is subject to validation. With exponential increase in PLC-based manufacturing systems, the FDA has begun to place strict requirements on computer validation. A computer system consists of hardware, that is, physical and calibration devices, sensors, input/output devices, transducers, or equipment, and its companion software, which is used to generate records, instructions, or data. Source codes and supporting software documentation used in drug process control is considered to be part of the master production and control records under cGMP interpretation. The computer systems may comprise

- Computer-integrated manufacturing
- Analytical instrumentation and automated laboratory practices
- Computer-controlled electronic signature systems
- Computer-integrated packaging operations
- Laboratory information-management systems
- Computer systems for good clinical practice
- Computer-assisted medical devices

The categories listed above require qualification and validation documentation. It is advisable that process automation and companion computer-integrated manufacturing operations not be initiated until sufficient prospective and concurrent validation studies have been completed.

The requirements for hardware validation are identical to those of any other equipment in use, comprising the OQ/IQ/PQ cycle, except that in the PQ, it is the test of software used. The software validation comprises functional testing, in which defined inputs produce outputs that meet expectations or specifications; a thorough examination of source codes, database designs, programming standards, control methods, and support documentation; or a quality-assurance program that includes alternate plans, contingency practices, record retrieval, and security practices

I. Documentation Standards

The cliché of the three Ds — documents, documents, and more documents — is apt for FDA PAI inspections. Historically, the regulatory agencies have relied heavily on cross-checking documents to ascertain the state of compliance with the cGMP regulations. The documents of critical importance are the batch records that contain detailed information about the batch history. It is often difficult for a firm to "fudge" these documents, although many have tried. What is important to understand here is that the entire batch record is cross-checked with the purchase requisitions, delivery documents, testing documents, and final release documents. It is almost impossible to create a system that would fool the FDA inspectors. The firms are advises that a low level of due diligence will expose the trial of doing paperwork. Included in the batch records are the date of manufacture, the identity of major equipment and lines used, specific identification of each batch of component or in-process material used, weights and measures of components used in the course of processing, in-process and laboratory control results, inspection of the packaging and labeling area before and after use, a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing, complete labeling control records, including specimens or copies of all labeling used, description of drug product containers and closures, any sampling performed, identification of the persons performing and directly supervising or checking each significant step in the operation, any deviation report resulting from an investigation made according to 21 CFR 211.192, and results of examinations made in accordance with 21 CFR 211.134 (packaging and labeling inspections).

Change control is the procedural system through which changes are reviewed, justified, documented, approved, and implemented in conformance with regulatory and corporate requirements. To support a strong change control system, the firms must have a series of documents available that includes a summary of all changes made to date that affect the manufacturing process being considered for approval; individual reports that are written to review, justify, approve, and implement specific changes that affect the manufacturing process being considered for approval; any change control reports for facilities, manufacturing processes, and cleaning processes; or analytical laboratory methods that are related to the NDA/ANDA process being submitted. As it is a routine that changes are made in the development timeline, a rigid change control system may not work all the time. It is therefore recommended that the firms must have available for the FDA investigators a history of changes made, along with justification for the changes. It is important for the firms to know that the investigators arriving at the site may not have a copy of the filing made to the FDA, such as the CMC section of the application. Firms are advised to have a "third" copy available. The requirements of the CMC section are given below; these requirements also apply to supplements, except that the information required in the supplement is limited to that needed to support the change being submitted.

1. Batch production record
2. Specifications and test procedures for each component and for the drug product
3. Names and addresses of the sources of the active and noncompendial inactive components

and of the container closure system for the drug product
4. Results of any test performed on the components used in the manufacture of the drug product and on the drug product
5. Name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility
6. Proposed or actual master production record, including a description of the equipment to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product must be provided for all initial NDAs; ANDAs must contain a proposed or actual master production record

1. Development History Report

A historic summary of the development of the product serves many purposes. The foremost purpose is to apprise the investigators of the scope of inspection. The investigators learn more about the product from the history of its development than from the analysis report of the finished product. This shows the awareness of the firm about the development process. This document should include a description of the API, the formulation, and the analytical methods. These sections should be clearly marked or presented in separate binders. The summary section should highlight how the biobatch is linked to the full-scale batch with respect to validation and scale-up of production. This section also offers an opportunity for the firm to address the issues that it considers critical.

2. Deviation Records

Deviations are inevitable, whether they occur in the production or the testing of the product; obviously, a broader standard is used during development than in full-scale production. The important thing is that all deviations should be recorded, a justification should be provided for the decision to deviate, and a description of its potential effect on the quality of product should be provided. Of most significance to the FDA is the reason for entering into a deviation: Is it because the process was not adequately characterized or validated? Or was it because of inevitable circumstances, such as a breakdown in the system? A logbook describing deviations is one way the firm may show to the FDA is diligence in ensuring compliance with the cGMP regulations. Nothing makes the FDA more suspicious than a blank log stating that there were no deviations. In addition, these log reports offer an excellent medium for internal QA audits. Firms need to understand that the purpose of cGMP compliance is ensuring the quality and safety of the product, not necessarily adhering to a particular process or composition. Obviously, the requirements of validation make it necessary that any deviation converted into regular practice must be properly validated.

3. Installation, Operational, and Performance Qualification

The IQ/OQ/PQ documents pertaining to all manufacturing equipment, analytical equipment, or systems should be available for inspection. In many instances, firms consider their development laboratories as not needing to be as rigidly compliant for these documentation requirements as their manufacturing facilities are. This creates serious problems at PAI if the development laboratory produces a biobatch. Furthermore, the process or method transfer becomes a serious problem if unqualified equipment or processes are used in the development cycle. Firms are strongly urged to treat their development laboratory as if they were cGMP-compliant facilities.

4. Organizational Chart

Organizational charts establish that an adequate number of personnel are available to perform and supervise the manufacture, processing, packaging, or holding of a drug product (21 CFR 211.25), that a proper chain of responsibility has been established in supervisors of manufacturing processes, and that there is appropriate separation of responsibilities for manufacturing operations and the quality unit. These charts should be available for both the development organizations and the commercial manufacturing organizations.

5. Products List

To evaluate how the product submitted may be affected by the manufacturing of other products in the same premises, a complete list of all products manufactured should be provided to the PAI team on the first day of inspection. The FDA considers cross-contamination issues critical; should there be a serious objection raised, the PAI team will refuse to continue the audit. Firms are strongly urged to review the cGMP guidelines and the guidance documents provided by the FDA: Some basic rules about the cephalosporins, penicillins, hormones, and biological products are well known; however, when in doubt, do not hesitate to write the FDA to seek clarification before beginning the production of a new product. It is noteworthy that a single batch of a forbidden entity in the premises

may render the premises unsuitable forever if proper validation could not be performed. For example, if a penicillin or cephalosporin product is manufactured on the premises, this premises can no longer be used for any other product, as it would be difficult to prove the absence of contaminants.

6. Drawings

Site plan drawings should be available for facilities used in clinical trial material production as well as for those at which commercial products will be produced. These drawings quickly show how the facility is constructed and controlled and include the floor plan, which shows the proper segregation of areas by walls, airlocks, and doors; these plans are useful to demonstrate people and equipment flow, showing that clean personnel and equipment do not cross paths with dirty personnel and equipment. Also, there should be a broader facility and grounds plan showing the relative position and location of various buildings in the facility. This is particularly useful where multiple building are used to finish the product or to test it, as the security of the batch in transit and the possibility of contamination are key issues to be resolved. In addition, drawings of the utility systems, such as the heating, ventilation, and air-conditioning systems and water systems, should be available. Firms are advised that they may request the FDA to review these drawings before the visit, perhaps at the time of installation, to make sure that the basic guidelines are adhered to.

7. Stability Data

Some of the most significant data that the PAI team confirm is the stability profile of the product; most likely the raw data would be examined if the presentation of the summary data appears flawed.

8. SOPs

SOPs relevant to basic systems and operations should be provided in a neatly arranged folder starting with the master validation plan, product, personnel, and process management. A comprehensive index should be attached.

9. Training Records

It is a cGMP requirement (21 CFR 211.25 a, b) that personnel have education, training, or experience that enables them to perform their assigned task. These training records should include the training curriculum for each individual, as well as the list of completed courses. These records should be made available for all personnel who manufacture, process, package, test, or release clinical trial materials and the commercial product. Firms are strongly reminded that in most inspections the FDA finds this to be one of the weakest areas. For example, some of the common FDA citations for training violations include lack of formal training documentation, lack of training in GMP regulations on an ongoing basis, lack of a formal job function training program, lack of a system for evaluating or monitoring employees to ensure that training was effective, no provision for retraining individuals on a periodic basis to ensure that employees remain familiar with the requirements applicable to them, no provision for training employees on recently revised procedures, and no provision for ensuring that employees were trained before they perform job functions. Training records should also include details about how the new employees are trained to follow the company's SOPs, rules, and other regulations. The SOP reading and understanding records, therefore, form vital evidence that the FDA examines to ensure that all employees have received adequate training in performing their tasks. Awareness and understanding of what is considered critical depends on the role the employee plays; for example, compliance with good laboratory pratices (GLP) or good clinical practice may be relevant to some, but not all, employees. Safety training, job function training, and documentation training are additional requirements.

10. Validation Records

Validation protocols may include test parameters, product characteristics, production equipment specifications and settings, and decision points on what constitutes acceptable test results. Three types of validation protocols should be available during the PAI: cleaning, manufacturing process, and analytical methods. Any data associated with a completed protocol should also be made available. Also, if there had been any retrospective validation, these data should also be available.

11. Technology Transfer and Scale-Up

The goal of technology transfer and scale-up is to show, through process control, that any modifications made from conception to implementation have been appropriately evaluated and documented and that the product is safe, pure, and effective. The technology transfer master plan comprises three components: the documents, the writing style, and the illustration of equivalents. The development stage documents are often abbreviated, and the files are not necessarily as complete as in the case of full-scale production; also in addition, the language used often differs as the audience changes from a scientist to a line worker. It is important also to show how the equivalent processes were selected; for example, when using a small dryer, how can the use of large fluid bed dryer be labeled as equivalent?

12. Quality Policy

The quality policy is a global document for the company that covers such issues as recalls, employee training and certification, and overall impact analysis of product and process changes. Customer expectations, materials specifications, and laws and regulations may also affect the number of personnel needed and the way quality functions are subdivided into manageable work units. Of importance for inclusion in the quality systems description are the documenting controls, including clearance and issuance of production records, procedures, specifications, and so forth; internal and vendor audits; sampling, examination, and approval of materials, including packaging and labeling (often administered by the laboratory component of the department); Material Review Board representatives; verifying yields and other critical production data through production record audits; finished product release; accompanying FDA investigators and external auditors; administering or contributing to cGMP, safety, or other required training programs; ensuring the investigations of product failures, process deviations, laboratory out-of-specification findings, and consumer complaints; monitoring approval and implementation of corrective action plans and change controls; on-site verification of the performance of critical production operations such as clearing labeling equipment and lines; review and approval of the product development records and documents transferring a product from development to commercial production; validation/qualification protocols and summary reports acceptance; and annual cGMP review. In addition, some functions are delegated to the engineering group to complete, and these include statistical process control and trend analyses; calibration of instruments and equipment, including out-of-specification follow-up; and analysis of reports of extraordinary maintenance and preventative maintenance failures.

13. Vendor Approval

The ISO 9001 and ISO 9002 Quality Standards require manufacturers to select vendors on the basis of their ability to meet purchase specifications. By ISO 9004 definition, this includes meeting regulatory requirements and safety standards. The FDA's cGMP regulations 21 CFR 211.84(a) through (e) require a manufacturer to test and approve or reject components, drug product containers, and closures. 21 CFR 211.84(d)(2) requires the manufacturer to test each component for conformity with written specifications for purity, strength, and quality or to accept the supplier's report of analysis. 21 CFR 211.84(d)(3) requires the manufacturer to test containers and closures for conformance with all appropriate written procedures or to accept the supplier's report of analysis. Reports showing compliance with firm's vendor approval policy are required at the time of PAI.

14. Outside Contractors

When any work is contracted out, whether in manufacture or testing phase, the FDA will hold the firm where the deviation or deviations occurred responsible for violations of the cGMP regulations (21 CFR 210 and 211) that pertain to those services. However, the contractor and the application holder will be held jointly responsible for processes performed by the contractor to the extent that each party contributed to the violations. Performance of each party will be considered in determining whether one or both parties are subject to regulatory action for failure to comply with cGMPs. It is in the best interest of the applicant to perform due diligence in the selection of any contractor, as well as to audit the contractors to ensure they meet the regulatory requirements and the contractual commitments.

5 Formulation Considerations of Liquid Products

Liquid formulations offer many advantages, from ease in dosing to ease in administration (easy to swallow), and myriad possibilities of innovative drug delivery systems. One of the most desirable features of liquid formulations, particularly the solution forms, is the relatively lower importance of bioavailability considerations, as the drug molecules are already in the dispersed phase, removing many rate-limiting steps in the absorption of drugs. For the purpose of this volume, liquid formulations include formulations that have liquid characteristics, meaning they can flow and thus include clear liquids, suspensions, and extemporaneous powder suspensions (which could easily be classified as uncompressed solids but for the stability considerations postreconstitution, which are common to liquid preparations). However, all of the advantages of liquid dosage forms are balanced by the many problems in their formulation. These include stability problems, taste masking needs, phase separations, and so forth, all of which require highly specialized formulation techniques.

I. SOLUBILITY

The amount of active drug dissolved per unit of a solvent or liquid base is a critical parameter subject to many factors including temperature, presence of electrolytes (salting-out effect), complexation with other components, state of crystallinity (such as amorphous), nature of crystals (inclusion or imperfections), hydration, or salvation, and so forth. One of the most important studies conducted on new chemical entities is the solubility characteristics, phase conversion studies, and saturation limits under different conditions. Where the amount of drug is above saturation solubility, an equilibrium between the solution (monomolecular dispersion) is established with undissolved particles (often multimolecular dispersions), the direction and extent of which are governed by many physicochemical factors. Because the absorption of drugs takes place only from a monomolecular dispersion (except those instances of pinocytosis, etc.), the equilibrium of the two states is critical to drug absorption. A large number of pH-adjusting buffers are used in the liquid products to modify the solubility of drugs as well as to provide the most optimal pH for drug absorption and drug stability. The dielectric constant of the solvent (or composite dispersion phase) is important in determining the solubility. With available values of dielectric constant available, for both pure systems and binary systems, it is easy to project the solubility characteristics of many new drugs. Another factor determining the solubility of drugs is the degree of solubilization in the dispersion phase.

Solubilization is defined as spontaneous passage of poorly water-soluble drugs into an aqueous solution of a detergent, the mechanism being entrapment of drug molecules in the micelles of surface active agent. As a result, many liquid preparations contain surfactants, not only to solubilize but also to "wet" the powders to allow better mixing with liquid phase. Because the critical micelle concentration of surfactants is highly dependent on the presence of other polar or dielectric molecules, the use of surfactants to solubilized drugs requires extensive compatability studies. The most common solubilizers used include polyoxyethylene sorbital, fatty acid esters, polyoxyethylene monoalklyl ethers, sucrose monoesters, lanolin esters and ethers, and so forth.

Complexation with other components of formulation can give rise to enhanced or reduced solubility. Organic compounds in solution generally tend to associate with each other to some extent, but these are weak bonds, and the complex readily disassociates. Where the drug forms a stronger complex, such as with caffeine or other binders, solubility can be extensively altered. Some polyols are known to disrupt complexes, reducing the solubility. Often complexation results in loss of active drug or a preservative used in the system, leading to serious stability problems. Examples of complexation include when xanthines, polyvinyl pyrrolidone, and so on bind to drugs.

Hydrotrophy is defined as an increase in solubility in water caused by presence of large amounts of additives. It is another type of "solubilization," except the solubilizing agent is not necessarily a surfactant. The phenomenon is closer to complexation, but the change in solvent characteristics play a significant role as well. In general, the quantity of other components must be in the range of 20 to 50% to induce hydrotrophy.

II. CHEMICAL MODIFICATION

Many poorly soluble drugs can be made more water soluble by modifying their chemistry, such as introducing by a hydrophilic group on the molecule. Salts and derivates of poorly soluble drugs are widely used, and modification requires a careful selection because different salts and

forms may not have the same chemical stability, and also because the biologic activity may be modified.

III. PRESERVATION

Preservatives are almost always a part of liquid formulations unless there is sufficient preservative efficacy in the formulation itself, such as due to high sugar content, presence of antimicrobial drugs, or solvents that inhibit growth such as alcohol. In all instances a preservative efficacy challenge is needed to prove adequate protection against the growth of microorganisms during the shelf-life and use of the product (such as in the case of reconstituted powder suspensions). A large number of approved preservatives are available, including such universal preservatives as parabens, to protect liquid preparations. Among the acidic group, the most prominent preservatives are phenol, chlorocresol, O-pheyl phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and its salts, boric acid and its salts, and sorbic acid and its salts; neutral preservatives include chlorbutanol, benzyl alcohol, and beta-phenylethyl alcohol; mercurial preservatives include thiomersal, phenylmercuric acetate, and nitrate; and nitromersol and quarternary compounds include benzalkonium chloride and cetylpyridinium chloride. The admissible levels of preservatives are defined in the pharmacopoeia. It should be noted that although preservatives provide an essential function, they often cause an unpleasant taste and allergic reactions in some individuals, requiring proper labeling of all products containing preservatives.

IV. SWEETENING AGENTS

Because taste is of prime importance in the administration of liquid products, sweetening agents ranging from sugar to potassium acesulfame are widely used; appropriate warnings are required when using artificial sweetening agents. Often a combination of sweetening agents is used, in combination with various flavors (which are often included to make the product more palatable), to impart the best taste. When formulating granules for dispersion, solid flavors are preferred.

V. FLAVORS

There are four basic sensations: salty, bitter, sweet, and sour. A combination of efforts is required to mask these tastes. For example, menthol and chloroform act as desensitizing agents; a large number of natural and artificial flavors and their combinations are available to mask the bitterness most often found in organic compounds. Most formulators refer the selection of compatible flavors to companies manufacturing these flavors, as they may allow use of their drug master file (DMF) for the purpose of filing regulatory applications. The formulator is referred to Givaudan (http://www.givaudan.com/), International Flavors and Fragrances (http://www.iff.com), and Flavors of North America (http://www.fonaflavors.com). Detailed information about other companies can be obtained from the National Association of Flavor and Fragrances (http://www.naffs.org/naffs/public/members.htm). It is noteworthy that as of the end of 2003, all foreign manufacturers of flavors are required to file a registration with the U.S. Food and Drug Administration under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

VI. VISCOSITY

Because the flow of liquid for dispensing and dosing is important, an appropriate control of viscosity is required to prevent the liquid from running and, at the same time, to allow good dosing control; many thickening agents are available including carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone, and sugar. Because of the significant opportunities available for interacting with salts and other formulation ingredients, the viscosity control should be studied in the final formulation and over the shelf life of the product.

VII. APPEARANCE

The appearance or color of liquid products is often synchronized with the flavors used; for example green or blue for mint, red for berry, and so forth. Because the amount of dyestuffs allowed in pharmaceutical products is strongly regulated, this presents problems — especially where there is a need to mask features of a preparation. In some instances, solutions are made to "sparkle" by passing them through a filtration process. Often, adsorbents are used in the liquid preparations to remove fine particles, imparting a greater clarity to solutions. Filtration often presents problems, but with the help now available from major filter manufacturers, most problems can be readily solved. The formulators are urged to consult these commercial suppliers.

VIII. CHEMICAL STABILITY

Drugs are more unstable in solution or liquid dispersion than they are in solid state because the molecular interactions are more plausible in liquid surroundings.

IX. PHYSICAL STABILITY

Physically stable liquid products are supposed to retain their color, viscosity, clarity, taste, and odor throughout the shelf life; however, the limits of the specifications for

physical attributes are often kept flexible to allow for subjective evaluation criteria often involved and for inevitable, inconsequential, changes in the physical characteristics of these products. Ideally, a freshly prepared product is used as the reference standard; alternately, many companies develop more objective evaluation criteria using instrumental evaluation instead of subjective evaluation. Similar to chemical stability, physical stability can be significantly altered by the packaging type and design; as a result, the New Drug Application for every product requires a package interaction description; obviously, final stability data are to be developed in the final package form. Although glass bottles are fairly resistant to many products, caps and liners are often not. Even the integrity of the caps needs to be evaluated, applying exact torque in closing the bottles intended for stability evaluation; this is important to prevent any cap breakage that might adversely affect stability.

X. RAW MATERIAL

Raw material specifications are more important in liquid products, as the contaminants can adversely affect the formulation more than in solid dosage form. Also, the many features of a liquid product are controlled by including several raw materials such as sweeteners, thickening agents, and so forth, further complicating the matrixing of formulation at the development stage. The microbial quality of raw materials (both solid and liquid) needs to be critically evaluated. It is noteworthy that several raw materials used in liquid products may fall into the "food" category, and even though one is purchasing pharmaceutical-grade material, newly enacted laws in the United States require all foreign manufacturers to make a complete declaration of the composition of materials. Companies are encouraged to revise their specifications based on this additional information, to control the quality of raw materials more tightly.

Water is the most common raw material used, and it is recommended that the manufacturer fully comply with the standards of at least purified water for inclusion in the formulation, though there is no requirement. Efforts should be made to provide as much microbial-free water as possible; this can be readily achieved by installing a loop system in which the incoming water is first subjected to ultraviolet sterilizer, carbon filter, demineralizer, and a 5-micron filter, and then sent to a heated tank, from which it is passed again through an ultraviolet sterilizer and then a 0.22-micron filter before bringing it into the product; water coming out of the 5-micron filter can be circulated. When using a loop, it is important to establish methods for draining the dead water in the tap and the loop before using it. Also make sure that the flow rate of water does not exceed the sterilizing capacity of the ultraviolet systems installed.

XI. MANUFACTURING EQUIPMENT

Fully sanitizable stainless steel 314 or better quality is recommended. Equipment must be cleaned or sterilized; appropriate disinfectants include dilute solutions of hydrogen peroxide, phenol derivatives, and peracetic acid. Equipment lines can be sterilized by using alcohol, boiling water, autoclaving, steam, or dry heat. Where lids are used, be cautious of the condensate, which may be a source of microbial contamination. Operators must conform to all sanitary presentation requirements, including head covering, gloves, and face masks. Use of portable laminar flow hoods to expose ingredients before addition is often desirable.

XII. MANUFACTURING DIRECTIONS

Provided in this volume are hundreds of formulations with manufacturing directions; in some instances, for the sake of brevity, general details are left out that pertain to basic compounding techniques. For example, the order of addition and techniques of adding solutes to a liquid tank can be very important. Flavors are generally added after first mixing them in a smaller volume of the solvent or liquid base and rinsing them with a portion of liquid as well. This also holds for all other additions, particularly those of smaller quantities of ingredients. Proper mixing is validated; however, unlike solid mixing, where overmixing may result in segregation, the problems in liquid mixing pertain to air entrapment. Appropriate temperature of the liquid phase is often important to ensure that there is no precipitation of the solute added. Classic examples include use of syrup base, which must be heated to bring it to proper viscosity and to allow proper mixing. Parabens, when used as preservatives, must be dissolved in hot water because the quantity used is small and can be readily lost if complete dissolution is not ensured. In most instances, small quantities of solutes should be predissolved in a smaller quantity of solvent before adding it to the main tank. It is customary to bring the batch to the final volume of weight. The gravimetric adjustments are preferred, as they can be done while taring the vessel. Problems arise when solvents like alcohol are used wherein volume contraction and density are subject to temperature changes. Also, formulations are often presented in a volumetric format and require careful conversion calculation, especially where one or two components are used to compensate for the amount of active used (e.g., based on potency factors).

XIII. PACKAGING

Filling of liquid products is determined by their viscosity, surface tension, foam-producing, and compatibility with filling machine components. Liquids are often filled at a higher temperature to allow better flow. In most instances,

some type of piston filling and delivery is used to fill bottles, for which proper control of volume is required. The filling can be done on the basis of fixed volume or on the level of fill in the container. The filling can be accomplished through positive pressure or through a vacuum created in the container. If the latter is used, care should be taken not to lose any volatile components through the vacuum process; proper validation is required. Liquid product exposed to environment should be protected and filled under a laminar flow hood where possible. All points of contact of product to the environment should be similarly protected; however, once the product has been filled and capped, the bottles can be safely taken to an uncontrolled environment. In most instances, either plastic or aluminum caps are applied to bottles. The liners used in the caps should demonstrate full compatibility with the product, including any adhesive used. Proper torque should be applied to ensure a tight seal. Pilfer-evident packaging where used must comply with the regulatory requirements. It is not uncommon for syrups to crystallize out at the edge of the bottles, which the consumer might think a defect. Efforts should be made to formulate products to avoid this type of crystallization; use of sugar-free formulations is becoming more acceptable and offers a good alternate. However, taste masking without using sugar or liquid glucose remains a challenge. Stability testing in final packaged containers should include trial shipment runs as well to ensure that the caps do not come off or leak during the shipment.

XIV. PARTICLE SIZE AND SHAPE

When suspensions are formulated to provide a stable system, the particle size becomes critical. Flocculated suspensions also require careful particle size control either in the process of manufacturing or in the starting material. Equally important is the crystal habit — the outward appearance of an agglomeration of crystals. Crystal structure can be altered during the manufacturing process, particularly if the product is subject to temperature cycling, and this can alter the stability of suspensions.

XV. SUSPENSIONS

Suspensions are manufactured either by a precipitation or by dispersed methods requiring use of suspending agents whose characteristic can significantly change because of the presence of other components such as electrolytes.

XVI. EMULSIONS

Heterogeneous systems comprising emulsions offer greater difficulties in manufacturing, where not only is a careful calculation of formulation additives such as surfactants required but also the manufacturing techniques such as mixing times, intensity of mixing, and temperature become critical in the formation of proper emulsion of the stable type. Microemulsion manufacturing requires special equipment, and recently the use of nanoparticles has created a need for highly specialized handling systems. Homogenizers are used to emulsify liquids along with ultrasonifiers and colloid mills. In some instances, spontaneous emulsification is obtained by a careful order of mixing. The choice of emulsifying agent depends on the type of emulsion desired and determined by the use of hydrophilic–lipophilic balance evaluation. The temperature at which an emulsion is formed can often affect the particle size and, thus, later, the tendency to coalesce or break. Auxiliary emulsification aids include use of fine solids. Hydrophilic colloids are commonly used to impart proper viscosity that enhances stability of emulsions. However, there is a tendency to build up viscosity with time in freshly prepared emulsions. The flow characteristics of emulsions are important and are determined by the emulsion's yield value. Consistency in the density character of emulsion is therefore important. Clear emulsions have a lower proportion of internal phase and require solubilization techniques more frequently than do opaque emulsions. The antimicrobial preservatives used in emulsions are selected on the basis of the type of emulsion manufactured (oil-in-water or water-in-oil). Because water is one of the phases often encountered in emulsions, these must be properly preserved. Classical preservatives are used, but care must be exercised in not selecting preservatives that might interact with surfactants; get adsorbed onto the packaging material such as plastic bottles, caps, or cap liners; and be lost to a point at which they are rendered inactive. Parabens remain a good choice. The presence of oil phase also requires inclusion of antioxidants where necessary, and these may include such examples as gallic acid, propyl gallate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbic acid, sulfites, l-tocopherol, butyl phenol, and so forth. Scaling up of emulsion formulations from laboratory scale to manufacturing scales often presents significant problems related to temperature distribution studies; often the two phases are mixed at a specific temperature that may change during the mixing process and thus require a certain mixing rate. Stability testing of emulsions is subject to different protocols than those used for other liquid products; for example, higher-temperature studies may cause an emulsion to break but may not be reflective of the log-linear effect of temperature but, rather, of phase change or inversion. Centrifugation is a common technique to study emulsion stability, and so is the agitation test, which may cause suspended phases to coalesce. Of prime importance in the stability evaluation of emulsions are the phase separation, viscosity changes, changes in

light reflection, viscosity, particle size, electrical conductivity, and chemical composition.

XVII. POWDER FOR RECONSTITUTION

Whereas classically powder forms would fall under solids, they are included in liquids because of the requirements of formulation after the powder is reconstituted. In some instances, preservatives are required to protect the product during use by the patient. It is important to note that the FDA considers this phase of use of product a part of the product development strategy. The manufacturer must ensure label compliance through the use period, as indicated on the package and under the conditions prescribed, such as keeping it in a refrigerator. Whereas the instructions require the product to be stored in a refrigerator, product development should evaluate a wider range of temperatures, as the temperature inside the consumer's refrigerator may not correspond to the official definition of refrigeration. The method of granulation for the powders intended for resuspension before use is a traditional one, as is used in the preparation of uncompressed or even compressed solids; the difference here is obviously the consideration of the effects of stability on reconstitution, which may require addition of stabilizers. In general, the method of granulation requires wet massing, screening, drying, and screening again; fluid bed dryers may be used as well.

XVIII. NASAL SPRAY PRODUCTS

Nasal spray drug products contain therapeutically active ingredients (drug substances) that are dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, and buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or can be premetered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local or systemic effects. Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, controls of critical steps, intermediates, and drug product). These aspects should be considered carefully during the development program because changes can affect the ability of the product to deliver reproducible doses to patients throughout the product's shelf life. Some of the unique features of nasal sprays are listed below:

- Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition.
- Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice.
- The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product.
- The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays, depending on the intended site of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical procedures.

A. Inhalation Solutions and Suspensions

Inhalation solution and suspension drug products are typically aqueous-based formulations that contain therapeutically active ingredients and can also contain additional excipients. Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local or systemic effects and are used with a specified nebulizer. Unit-dose presentation is recommended for these drug products to prevent microbial contamination during use. The container closure system for these drug products consists of the container and closure and can include protective packaging such as foil overwrap.

B. Inhalation Sprays

An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous based and, by definition, do not contain any propellant. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are intended for delivery to the lungs by oral inhalation for local or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations. The use of preservatives or stabilizing agents in inhalation spray formulations is discouraged. If these excipients are included in a formulation, their use should be justified by assessment in a clinical setting to ensure the safety and tolerability of the drug product. The dose is delivered by the integral pump com-

ponents of the container closure system to the lungs by oral inhalation for local or systemic effects. The container closure system of these drug products consists of the container, closure, and pump, and it can also include protective packaging. Current container closure system designs for inhalation spray drug products include both premetered and device-metered presentations using mechanical or power assistance or energy from patient inspiration for production of the spray plume. Premetered presentations contain previously measured doses or a dose fraction in some type of units (e.g., single or multiple blisters or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Typical device-metered units have a reservoir containing formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient. Inhalation spray and nasal spray drug products have many similarities. Many of the characteristics for nasal sprays are also characteristic of inhalation spray drug products. Moreover, the potential wide array of inhalation spray drug product designs with unique characteristics will present a variety of development challenges. Regardless of the design, the most crucial attributes are the reproducibility of the dose, the spray plume, and the particle/droplet size distribution, as these parameters can affect the delivery of the drug substance to the intended biological target. Maintaining the reproducibility of these parameters through the expiration dating period and ensuring the sterility of the content and the functionality of the device (e.g., spray mechanism, electronic features, and sensors) through its lifetime under patient-use conditions will probably present the most formidable challenges. Therefore, changes in components of the drug product or changes in the manufacturer or manufacturing process that can affect these parameters should be carefully evaluated for their effect on the safety, clinical effectiveness, and stability of the product. If such changes are made subsequent to the preparation of the batches used in critical clinical, bioequivalence, or primary stability studies, adequate supportive comparative data should be provided to demonstrate equivalency in terms of safety, clinical effectiveness, and stability of the product.

C. Pump Delivery of Nasal Products

A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the delivery from the pump should be performed. The proper performance of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions. Pump spray weight delivery should be verified by the applicant for the drug product. In general, pump spray weight delivery acceptance criteria should control the weight of individual sprays to within "15 percent of the target weight" and their USP mean weight to within "10 percent of the target weight." However, for small-dosage pumps (e.g., 20 μL), other acceptance criteria may be justified. Acceptance testing for pump delivery on incoming pump lots can substitute for the release testing of pump delivery for the drug product, if justified. However, the acceptance criteria for pump delivery should be included in the drug product specification.

D. Spray Content Uniformity for Nasal Products

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. At most, two sprays per determination should be used except when the number of sprays per minimum dose specified in the product labeling is one. Then the number of sprays per determination should be one spray. To ensure reproducible *in vitro* dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, actuation force). The test can be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nasal actuator should be expressed both as the actual amount and as a percentage of label claim. This test is designed to demonstrate the uniformity of medication per spray (or minimum dose) consistent with the label claim, discharged from the nasal actuator, of an appropriate number (n = 10 from beginning and n = 10 from end) of containers from a batch. The primary purpose is to ensure spray content uniformity within the same container and among multiple containers of a batch. The following acceptance criteria are recommended, but alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of spray content uniformity. For acceptance of a batch:

- The amount of active ingredient per determination is not outside 80 to 120% of label claim for more than two of 20 determinations (10 from beginning and 10 from end) from 10 containers
- None of the determinations is outside 75 to 125% of the label claim
- The mean for each of the beginning and end determinations is not outside 85 to 115% of label claim

If the above acceptance criteria are not met because three to six of the 20 determinations are outside 80 to 120% of the label claim, 14 units but none are outside 75 to 125% of label claim, and the means for each of the beginning and end determinations are not outside 85 to 115% of label claim, an additional 20 containers should be sampled for second-tier testing.

For the second tier of testing of a batch, the acceptance criteria are met if

- The amount of active ingredient per determination is not outside 80 to 120% of the label claim for more than six of all 60 determinations
- None of the 60 determinations is outside 75 to 125% of label claim
- The mean for each of the beginning and end determinations are not outside 85 to 115% of label claim

E. Spray Pattern and Plume Geometry of Nasal Products

Characterization of spray pattern and plume geometry is important for evaluating the performance of the pump. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and the characteristics of the formulation. Spray pattern testing should be performed on a routine basis as a quality control for release of the drug product. However, the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter. The proposed test procedure for spray pattern should be provided in detail to allow duplication by FDA laboratories. For example, in the evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis is greater than *x* millimeters and the ratio of the longest to the shortest axes should lie in a specified range). Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst. Acceptance testing for spray pattern on incoming pump lots can substitute for the release testing of spray pattern for the drug product, if justified (e.g., spray patterns from pumps with drug product formulation and with the proposed simulating media are the same). However, the 15 acceptance criteria for spray pattern should be included in the drug product specification.

F. Droplet Size Distribution in Nasal Products

For both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet size distribution (e.g., three to four cut-off values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. If a laser diffraction method is used, droplet size distribution can be controlled in terms of ranges for the D_{10}, D_{50}, D_{90}, span $[(D_{90}\text{-}D_{10})/D_{50}]$, and percentage of droplets less than 10 μm. Appropriate and validated or calibrated droplet-size analytical procedures should be described in sufficient detail to allow accurate assessment by agency laboratories (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, and beam width). For solution nasal sprays, acceptance testing for droplet size distribution on incoming pump lots with placebo formulation can substitute for the release testing of droplet size distribution for the drug product, if justified (i.e., droplet size distributions from pumps with drug product formulation and those with the placebo are the same). However, the acceptance criteria for droplet size distribution should be included in the drug product specification.

G. Particle Size Distribution for Nasal Suspensions

For suspension nasal sprays, the specification should include tests and acceptance criteria for the particle size distribution of the drug substance particles in the formulation. The quantitative procedure should be appropriately validated, if feasible, in terms of its sensitivity and ability to detect shifts that may occur in the distribution. When examining formulations containing suspending agents in the presence of suspended drug substance, when it is demonstrated that the currently available technology cannot be acceptably validated, a qualitative and semiquantitative method for examination of drug and aggregated drug particle size distribution can be used. Supportive data, along with available validation information, should be submitted. For example, microscopic evaluation can be used, and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

XIV. EMULSIFICATION AND SOLUBILIZATION

To solubilize insoluble lypophilic or hydrophobic active substances in an aqueous medium, BASF Pharmaceutical

Excipients offer several possibilities and mechanisms. For microemulsions, Cremophor RH 40, Cremophor EL, and Solutol HS 15 act as surface active solubilizers in water and form the structures of micelles. The micelle that envelops the active substance is so small that it is invisible, or perhaps visible in the form of opalescence. Typical fields of application are oil-soluble vitamins, antimycotics of the miconazole type, mouth disinfectants (e.g., hexiditin), and etherian oils or fragrances. Solutol HS 15 is recommended for parenteral use of this solubilizing system and has been specially developed for this purpose.

XV. COMPLEXING

The soluble Kollidon products form reversible complexes with many hydrophobic active substances, and clear solutions in water are thus obtained. This may be affected by the molecular weight. The longer the chains or the higher the K-value of the Kollidon type are, the stronger the solubility effect is, and thus the greater the solubility that can be obtained by the active substance. In practice, this effect was mostly exploited for the solubilization of antibiotics in human and veterinary medicine. There are also restrictions on the use of this substance in human parenterals. In many countries the K-value must not exceed 18, and there is also a restriction on the amount to be used for each dose administered in intramuscular application.

XVI. HYDROPHILIZATION

Active substances can also be solubilized by Lutrol F 68 in addition to the Cremophor and Kollidon products. The mechanism is probably based, for the most part, on the principle of hydrophilization. Micelle formation is certainly of minor significance, if it exists at all.

XVII. STABILIZING SUSPENSIONS

Various BASF pharmaceutical excipients with different functions can be used for stabilizing suspensions. The following groups of products can be offered for stabilizing oral and topical suspensions. Soluble Kollidon products can be used at low concentrations; that is, at 2 to 5%, Kollidon 90 F suffices to stabilize aqueous suspensions. A combination consisting of 2% Kollidon 90 F and 5 to 9% Kollidon CL-M has proved to be an effective system for stabilizing suspensions. Kollidon 30 is also used for this purpose. It can be combined with all conventional suspension stabilizers (thickeners, surfactants, etc.). The use of Kollidon CL-M as a suspension stabilizer has nothing whatever to do with the principle of increasing the viscosity. The addition of 5 to 9% Kollidon CL-M has practically no effect in changing the viscosity, but it strongly reduces the rate of sedimentation and facilitates the redispersability, in particular — an effect that is consistent with the low viscosity. One of the reasons for this Kollidon CL-M effect is its low (bulk) density, which is only half of that of conventional crospovidone (e.g., Kollidon CL). The polyoxamers, Lutrol F 68 and Lutrol F 127, in concentrations of 2 to 5%, expressed in terms of the final weight of the suspension, offer a further opportunity of stabilizing suspensions. They also do not increase viscosity when used in these amounts and can be combined with all other conventional suspension stabilizers.

Part II

Manufacturing Formulations

Abacavir Sulfate Oral Solution

Ziagen oral solution is for oral administration. One milliliter (1 mL) of Ziagen oral solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Abacavir, use abacavir hemisulfate	23.40
344.40	2	Sorbitol 70%	344.40
0.30	3	Sodium saccharin	0.30
2.00	4	Strawberry flavor	2.00
2.00	5	Banana flavor	2.00
q.s.	6	Sodium citrate dihydrate for pH adjustment	10.00
q.s.	7	Citric acid anhydrous for pH adjustment	7.00
1.50	8	Methyl paraben	1.50
0.18	9	Propyl paraben	0.18
50.00	10	Propylene glycol	50.00
q.s.	11	Hydrochlorie acid dilute for pH adjustment to 4.0	q.s.
q.s.	12	Sodium hydroxide for pH adjustment	q.s.

MANUFACTURING DIRECTIONS

1. The pH range for this solution is from 3.8 to 4.5.
2. Charge 40% of the propylene glycol to an appropriately sized stainless steel and add methylparaben and propylparaben with mixing, and mix until dissolved.
3. Charge purified water into a stainless steel manufacturing tank equipped with a suitable mixer to approximately 40% of final batch volume.
4. Add sorbitol solution to the manufacturing tank.
5. While mixing, add item 1 and mix until dissolved.
6. While continuing to mix the solution, the paraben/glycol solution, the remaining propylene glycol, artificial strawberry flavor, artificial banana flavor, saccharin sodium, citric acid anhydrous, and sodium citrate dihydrate are added and mixed until dissolved.
7. Turn off the mixer and bring the solution to a volume of 500 L, and mix until a homogeneous solution is achieved.
8. Measure and adjust pH to 3.8 to 4.5 with sodium hydroxide or hydrochloric acid.
9. Filter the solution through a clarifying filter into an appropriately sized receiving vessel.

Acetaminophen Rectal Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (Pluronic P105 44.21%, propylene glycol 52.635, water 3.16%)	q.s. to 1 L
50.00	2	Acetaminophen micronized	50.00

MANUFACTURING DIRECTIONS

1. Mill and screen the acetaminophen to further reduce the particle size.
2. Add the acetaminophen into a clean vessel.
3. Add propylene glycol to the vessel.
4. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Acetaminophen Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
739.0	1	Propylene glycol	739.0
90.0	2	Acetaminophen	90.0
17.5	3	Saccharin sodium powder	17.5
8.75	4	Sodium chloride	8.75
0.05	5	Dye red FD&C No. 40[a]	0.05
2.5	6	Water purified	2.5
2.0	7	Flavor wild cherry artifical	2.0
65.0	8	Alcohol (ethanol) 190 proof nonbeverage	65.0
q.s.	9	Water purified	q.s. to 1 L

[a] Check for local regulatory allowance to use red dyes.

MANUFACTURING DIRECTIONS

Caution: Ensure that the solution in the tank never exceeds 65˚C.

1. Add 739 g propylene glycol to jacketed mixing tank and start heating with slow mixing.
2. Dissolve dye in 2.5 mL purified water and add to tank while mixing. Rinse container with small amount of purified water and add to tank.
3. While mixing, add acetaminophen, saccharin sodium, and sodium chloride.
4. Hold at 60˚ to 65˚C with continued moderate mixing until it is all in solution.
5. Force cool to less than 30˚C with slow mixing.
6. Blend flavor with alcohol and add to tank with slow mixing.
7. Add purified water with mixing q.s. to make 1 L.
8. Mix well with moderate agitation until uniform.
9. Filter through 8-micron Millipore membrane (or equivalent).

Acetaminophen Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
250.00	1	Acetaminophen micronized, 2.0% excess	51.00
2500.00	2	Sucrose	500.00
5.00	3	Methyl paraben	1.00
1.500	4	Propyl paraben	0.30
0.300	5	Sodium citrate	0.06
35.00	6	Glycerin (Glycerol)	7.00
400.00	7	Glycerin (Glycerol)	80.00
2000.00	8	Sorbitol (70%)	400.00
10.00	9	Xanthan gum (Keltrol F)	2.00
0.500	10	Dye	0.10
22.500	11	Flavor	4.50
3.500	12	Strawberry flavor	0.70
—	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Acetaminophen dispersion should be uniformly mixed or levigated. If acetaminophen dispersion is either added to hot syrup base or homogenized for a long time, flocculation may appear. While handling the syrup, mucilage, or drug dispersion, the handling loss should not be more than 1%. If the loss exceeds 1%, it may give poor suspension.
2. Add 180 g of item 13 to the mixer and heat to 90˚C.
3. Dissolve items 3 and item 4 while mixing. Add and dissolve item 2 while mixing. Cool down to about 50˚ to 55˚C.
4. Add and dissolve item 5 while mixing. Filter the syrup through T 1500 filters washed with item 13. Collect the syrup in clean stainless steel tank.
5. Disperse item 9 in item 6 in a separate stainless steel container. Add 40 g of hot item 13 (90˚C) at once while mixing. Mix for 20 minutes to make a homogeneous smooth mucilage.
6. Mix item 7 in 10 g of item 13 (25˚C) in a separate stainless steel container. Add item 1 while mixing with stirrer. Mix for 25 minutes to make uniform suspension.
7. Add sugar syrup and mucilage to the mixer. Rinse the container of mucilage with 15 g of item 13 and add the rinsings to the mixer. Cool to 25˚C while mixing.
8. Add item 1 dispersion to the mixer. Rinse the container of dispersion with 15 g of item 13 and add rinsings to the mixer. Check the suspension for uniformity of dispersion.
9. Mix for additional 5 minutes at 18 rpm, vacuum 0.5 bar if required.
10. Add item 8 to the mixer and mix for 10 minutes. Dissolve item 10 in 7 g of item 13 and add to the mixer.
11. Disperse item 11 in 7 g of item 13 and add to the mixer. Add item 12 to the mixer.
12. Add cold item 13 (25˚C) to make up the volume up to 1.0 L.
13. Homogenize for 5 minutes at low speed under vacuum 0.5 bar, 18 rpm, temperature 25˚C.
14. Check the dispersion for uniformity.
15. Check the pH. Limit 5.7 ± 0.5 at 25˚C. If required adjust the pH with 20% solution of Citric Acid or Sodium Citrate.
16. Transfer the suspension through 630 micron sieve after mixing for 5 minutes at 18-20 rpm, temperature NMT 25˚C, to the stainless steel storage tank.

Acetaminophen Suspension

Bill of Materials			
Scale (mg/10 mL)	**Item**	**Material Name**	**Quantity/L (g)**
500.00	1	Acetaminophen, powder	50.0
50.00	2	Citric acid, powder	5.0
50.00	3	Sodium citrate	5.00
500.00	4	Kollidon CL-M	50.0
10.00	5	Orange flavor	1.00
3000.00	6	Dextrose	300.0
q.s.	7	Water	589.0

MANUFACTURING DIRECTIONS

1. Prepare the solution of dextrose in water and add the other solid ingredients with stirring in the following sequence: citric acid, sodium citrate, orange flavor, Kollidon CL-M, and acetaminophen.
2. A white, homogeneous suspension is obtained.

Acetaminophen Syrup for Children

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
25.00	1	Acetaminophen, crystalline	25.00
300.00	2	Kollidon 25 or Kollidon 30	300.00
60.00	3	Glycerol	600.00
40.00	4	Sodium cyclamate	40.00
q.s.	5	Orange flavor	<01.0
q.s.	6	Raspberry flavor	2.00
q.s.	7	Water	575.00

MANUFACTURING DIRECTIONS

1. Dissolve Kollidon in water, add acetaminophen and cyclamate, heat to 50°C, and stir to obtain a clear solution.
2. Dissolve the flavors and mix with glycerol. The obtained syrup is a viscous, clear, sweet, and only slightly bitter liquid.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.0	1	Acetaminophen (Merck)	50.0
50.0	2	Sorbitol, crystalline	50.0
40.0	3	Cyclamate sodium	40.0
1.00	4	Strawberry flavor	1.00
200.0	5	Kollidon 25	200.0
150.0	6	Glycerol	150.0
200.0	7	1,2-Propylene glycol	200.0
310.0	8	Water	310.0

MANUFACTURING DIRECTIONS

1. Dissolve first Kollidon 25 and then the other solid components in the solvent mixture of glycerol, propylene glycol, and water.
2. The result is a clear solution of certain viscosity having only a slightly bitter taste. To prevent discoloration during storage, 0.2 to 0.5% cysteine could be added as an antioxidant.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
569.00	1	Sucrose (sugar granulated)	560.0
2.00	2	Sodium citrate dihydrate powder	2.0
1.00	3	Acid citric anhydrous powder	1.0
1.00	4	Saccharin sodium powder	1.0
1.00	5	Sodium chloride powder	1.0
204.00	6	Propylene glycol	204.0
35.00	7	Acetaminophen	35.0
77.11	8	Alcohol (ethanol) 190 proof	77.112
0.12	9	Flavor cherry artifical N59456/A	0.12
0.12	10	Dye red FD&C N40	0.10
q.s.	11	Water purified	400.0
q.s.	12	Filter aid hyflo	q.s.

MANUFACTURING DIRECTIONS

1. Add 300 mL purified water to a jacketed stainless steel mixing tank. Start heating.
2. Add sugar with mixing.
3. Heat to 60˚– 65˚C and hold. Mix for complete solution.
4. Add, while mixing, sodium citrate, citric acid, sodium saccharine, and sodium chloride. Mix for complete solution. Add propylene glycol by mixing.
5. Add acetaminophen powder with moderate mixing. Continue mixing at 60˚ – 65˚C for complete solution. Force cool to 25˚ – 30˚C with slow mixing.
6. Blend cherry flavor with approximately twice its volume of alcohol and add with mixing. Rinse the container with several portions of alcohol and add. Mix until uniform.
7. Dissolve red dye in approximately 4.0 g of slightly warmed (50˚ – 60˚C) purified water and add by mixing. Rinse the container twice with approximately 1.5 g purified water and add to step 6.
8. Mix until uniform. Adjust volume to 1 L with purified water. Mix well.
9. Add a small amount of hyflo filter aid to the mixing tank and continue to mix slowly while filtering.
10. Filter through press until sparkling clear. Use clarifying pad backed by lint-free filter paper.

Acetaminophen, Chlorpheniramine, and Pseudoephedrine Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
24.00	1	Acetaminophen (fine powder)	24.00
3.00	2	Pseudoephedrine HCl	3.00
0.44	3	Chlorpheniramine maleate, 10% excess	0.44
14.00	4	Ascorbic acid	14.00
2.40	5	Sodium hydroxide	2.40
1.00	6	Edatate disodium (sodium EDTA)	1.00
0.50	7	Saccharin sodium	0.50
2.00	8	Sodium metabisulphite (sodium disulfite)	2.00
80.00	9	Alcohol (ethanol 95%)	80.00
100.00	10	Propylene glycol	100.00
100.00	11	Sorbitol (70% solution)	100.00
250.00	12	Glycerin (glycerol)	250.00
300.00	13	Sucrose	300.00
0.04	14	Quinoline yellow	0.04
0.25	15	Pineapple flavor	0.25
q.s.	16	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 200.0 g of item 16 to the manufacturing vessel and heat to 90˚ to 95˚C.
2. Add item 13 while mixing at slow speed. Keep temperature at 90˚ to 95˚C.
3. Mix for 1 hour at high speed. Add items 12, 10, and 11 to the manufacturing vessel at step above while mixing at high speed. Mix for 10 minutes.
4. Cool the temperature to 50˚C while mixing at slow speed.
5. Add 70.0 g of item 9 to the syrup solution while mixing at slow speed. Load item 1 to the manufacturing vessel at step above while mixing at high speed.
6. Mix for 30 minutes to get clear solution. Check the clarity of the solution. Flush the solution with nitrogen gas for 5 minutes at 1 bar.
7. Add items 6, 8, 4, and 2 to the manufacturing vessel at step above while mixing at slow speed. Dissolve item 3 in 2.0 g of item 16 (at 25˚C) and check that solution is complete.
8. Add the solution to the manufacturing vessel while mixing at slow speed.
9. Dissolve item 15 in 10.0 g of item 9 in a stainless steel container and add to the manufacturing vessel while mixing at slow speed.
10. Dissolve items 5 and 7 in 20.0 g of item 16 (25˚C) and add to the manufacturing vessel at the step above while mixing at slow speed. Dissolve item 14 in 2.0 g of item 16 (at 25˚C).
11. Transfer the color solution to the manufacturing vessel while mixing at slow speed. Rinse the container of color solution with 2.0 g of item 16 (25˚C), then transfer the rinsing to the manufacturing vessel and mix for 5 minutes at high speed.
12. Make up the volume to 1.0 L with item 16, and finally, mix for 15 to 20 minutes at high speed.
13. Check and record the pH; the limit is 5.1 to 5.2. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
14. Assemble the filter press with 13.1 T 1000 12 sheets (K 800 14 sheets). Use changeover plate.
15. Wash the filters using about 200 L purified water (at 25˚C) by passing water through filters at 0.2 bar, and discard the washings.
16. Filter the syrup at 1.5 bar.
17. Recirculate about 20 to 30 mL syrup. Connect the hose to the manufacturing vessel and transfer the filtered syrup to the storage vessel.

Acyclovir Oral Suspension

Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
215.00	1	Acyclovir	43.00
5.00	2	Methyl paraben	1.00
1.00	3	Propyl paraben	0.20
75.00	4	Microcrystalline cellulose (Avicel RC-591)	15.00
750.00	5	Glycerin (glycerol)	150.00
2250.00	6	Sorbitol (70% solution)	450.00
20.00	7	Orange banana dry flavor	4.00
—	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Disperse item 1 in item 6. Keep stirring by stirrer for 1 hour.
2. Heat 333.33 g of item 8 in mixer to 90˚ to 95˚C. Dissolve items 2 and 3 while mixing. Cool to 30˚C.
3. Disperse items 4 and 5 in a stainless steel container and keep stirring for 1 hour.
4. Add step 3 into step 2 at 30˚C. Mix and homogenize for 5 minutes at high speed under vacuum 0.5 bar.
5. Add step 1 in to step 2 and mix for 5 minutes.
6. Disperse item 7 in 13.33 g of item 8. Add into step 2.
7. Make up the volume with item 8. Finally, homogenize for 5 minutes at high speed under vacuum 0.5 bar.

Acyclovir Oral Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Acyclovir	20.00
60.00	2	Kollidon CL-M	60.00
30.00	3	Kollidon 30	30.00
28.00	4	Sorbitol	28.00
0.50	5	Citric acid	0.50
q.s.	6	Preservative	q.s.
q.s.	7	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Suspend item 1 and item 2 in the solution of items 3 through 7.
2. Mix vigorously to suspend.
3. Fill.

Adapalene Solution

DIFFERIN® Solution, containing adapalene, is used for the topical treatment of a*cne vulgaris*. Each milliliter of DIFFERIN® Solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Adapalene	1.00
700.00	2	Polyethylene glycol 400	700.00
q.s.	3	Alcohol	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable mixing vessel. Stir.
2. Add and dissolve item 1 and mix.

Albendazole Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.000	1	Albendazole	20.00
7.500	2	Saccharin sodium	1.50
7.500	3	Potassium sorbate	1.50
550.000	4	Propylene glycol	110.00
15.000	5	Xanthan gum	3.00
2.500	6	Passion fruit flavor 502010A	0.50
7.500	7	Polysorbate 80 (Tween 80)	1.50
2.000	8	Citric acid	0.40
2.500	9	Vanilla dry flavor	0.50
2.500	10	Blood orange dry flavor	0.50
q.s. to 5 mL	11	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

This product dispersion should be uniformly mixed and levigated. Xanthan gum dispersion should be uniform and smooth.

1. Disperse items 1 and 6 in 100.0 g of item 4 in a stainless steel container, using stirrer.
2. Dissolve item 7 in 100.0 g of item 11 (50˚ to 60˚C) in a stainless steel container while stirring with the stirrer. Cool to 25˚ to 30˚C. Add in to step 1 while mixing.
3. Levigate to make smooth slurry and keep aside for 2.0 hours.
4. Make a slurry of item 5 in 10.0 g of item 4 in a stainless steel container while stirring with the stirrer. Add 200.0 g of item 11 (25˚ to 30˚C) while stirring and continue stirring for 30 minutes.
5. Dissolve item 8 in 10.0 g of item 11 (25˚ to 30˚C) in a stainless steel container, using a spatula.
6. Add 500.0 g of item 11 (25˚ to 30˚C) into mixer. Dissolve items 2 and 3 while mixing.
7. Add the content from step 1, 2, and 3 into step 4. Mix and homogenize at 25˚ to 30˚C, mixer speed 18 rpm, homogenizer high speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
8. Add items 9 and 10 in to step 4.
9. Mix and homogenize at 25˚ to 30˚C, mixer speed 18 rpm, homogenizer at high speed, and vacuum 0.4 to 0.6 bar for 15 minutes.
10. Make up the volume with item 11. Mix for 20 minutes.
11. Check the suspension for homogeneity. Transfer the suspension through a 630-micron sieve to stainless steel storage tank. It is very important that you do not store the bulk suspension more than 48 hours in the storage tank without stirring. Before sending for filling in packaging, stir no fewer than 30 minutes for uniform dispersion to avoid the problem of content uniformity.

Albendazole Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.00	1	Albendazole	40.00
1.25	2	Simethicone	0.24
5.00	3	Tween 80	1.00
15.00	4	Xanthan gum	3.00
1950.00	5	Sucrose	390.00
650.00	6	Sorbitol	130.00
20.00	7	Sodium benzoate	4.00
20.00	8	Potassium sorbate	4.00
3.00	9	Citric acid	0.60
q.s.	10	Flavor	q.s.
q.s.	11	Water purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge in a tank 20% of item 11 and heat to 90˚C.
2. Add and dissolve item 7; reduce temperature to 40˚C and add item 3.
3. In a separate vessel add and dissolve item 9 in a portion of item 11.
4. Add step 3 to step 2.
5. In a separate vessel disperse item 4 in 40% of item 11 at 65˚C and allow to hydrate to make it into a paste. Cool to room temperature.
6. Add to step 3 through a stainless steel filter.
7. In a separate vessel add and make a paste of items 1 (passed through #100 mesh), 3, and 6. Add to step above.
8. Add item 2. Stir well.
9. Add flavor and add item 11 to make up the volume.

Albuterol Inhalation Solution

Each milliliter of PROVENTIL Inhalation Solution 0.083% contains 0.83 mg albuterol (as 1.0 mg albuterol sulfate) in an isotonic aqueous solution containing sodium chloride and benzalkonium chloride; sulfuric acid is used to adjust the pH between 3 and 5. The 0.083% solution requires no dilution before administration by nebulization. PROVENTIL Inhalation Solution 0.083% contains no sulfiting agents. It is supplied in 3-mL HDPE bottles for unit-dose dispensing.

AccuNeb (albuterol sulfate) inhalation solution is supplied in two strengths in unit–dose vials. Each unit–dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile, aqueous solution. Sodium chloride is added to adjust isotonicity of the solution, and sulfuric acid is added to adjust the pH of the solution to 3.5.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.25	1	(R)-Albuterol, use albuterol sulfate	1.50
27.00	2	Sodium chlortide	27.00
q.s.	3	Sulfuric acid	q.s.
q.s.	4	Water purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge all items in a suitable stainless steel vessel and mix. Keep nitrogen flushing through-out, and also into item 4 before adding other ingredients.
2. Check and adjust pH, using sulfuric acid, to 3.50.
3. Fill.

Alpha-Bisabolol Aqueous Mouthwash Solution

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
2.00	1	Alpha-bisabolol, natural (BASF)	2.00
q.s.	2	Flavor	q.s.
25.00	3	Cremophor RH 40	25.00
50.00	4	Glycerol	50.00
1.00	5	Saccharin sodium	1.00
q.s.	6	Preservative	q.s.
922.0	7	Water	922.0

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 through 3 to about 60˚C and add slowly the warm solution of items 4 through 7 (60˚C).
2. This produces a clear, colorless liquid that has a low viscosity.

Alpha-Bisabolol Buccal or Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.20	1	Alpha-bisabolol, racemic (BASF)	1.20
10.00	2	Cremophor RH 40	10.00
0.10	3	Butylhydroxytoluene (BHT)	0.10
q.s.	4	Preservative	q.s.
990.0	5	Water	990.0

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 through 3 to about 60˚C.
2. Stir well and add slowly the warm solution of items 4 in 5. A clear solution is obtained.

Alpha-Bisabolol Ethanolic Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Alpha-bisabolol, racemic (BASF)	10.00
100.00	2	Flavor	100.00
60.00	3	Cremophor RH 40	60.00
10.00	4	Glycerol	10.00
2.00	5	Saccharin sodium	2.00
818.00	6	Ethanol, 96%	818.00

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 through 3 to about 60˚C and slowly add a warm solution of items 4 through 6.
2. This produces a clear, colorless liquid that can be diluted with water.

Alpha-Bisabolol Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	(-)Alpha-Bisabolol, natural (BASF)	5.00
50.00	2	Lutrol F 127 [1]	50.00
q.s.	3	Flavor	q.s.
100.00	4	Propylene glycol Pharma	100.00
300.00	5	Ethanol 96%	300.00
545.00	6	Water	545.00

MANUFACTURING DIRECTIONS

1. Prepare solution of items 1 through 5 and slowly add the water.
2. The clear, colorless solution should have a pH of 8. Do not adjust.

Aluminum Chloride Solution

Aluminum chloride (hexahydrate) 6.25% (w/v) in anhydrous ethyl alcohol (S.D. alcohol 40) 96% (v/v).

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
62.50	1	Aluminum chloride hexahydrate	62.50
q.s.	2	Alcohol anhydrous,	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable stainless steel container and mix.
2. Fill.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
405.00	1	Aluminum hydroxide gel	290.00
100.00	2	Magnesium hydroxide paste 30%	67.00
0.21	3	Ammonia solution 25%	0.042
0.053	4	Ammonia solution 25%	0.0106
10.00	5	Methyl paraben	2.00
0.25	6	Menthol	0.05
3.00	7	Propyl paraben	0.60
1.00	8	Peppermint oil	0.20
50.00	9	Propylene glycol	10.00
1.25	10	Saccharin sodium	0.25
150.00	11	Sorbitol (70% solution)	30.00
4.50	12	Sodium hypochlorite 5%	0.900
1.25	13	Sodium hypochlorite 5%	0.250
15.00	14	Magnesium aluminum silicate (Veegum HV)	3.000
—	15	Water, purified	q.s. to 1 L

Note. Quantity of the sodium hypochlorite solution to be adjusted according to the assay.

MANUFACTURING DIRECTIONS

1. Disperse item 14 in 60.0 g of hot item 15 (70° to 80°C) in stainless steel vessel, using stirrer.
2. Continue stirring for 30 minutes.
3. Transfer the dispersion into mixer (e.g., Krieger) vessel by vacuum and mix for 30 minutes at mixer speed 16/32.
4. Cool down to 30°C. Add 200.0 g of hot item 15 (70° to 80°C) into the mixer.
5. Mix and homogenize at rpm 1420 mixer speed 16/32, vacuum 0.5 bar for 30 minutes.
6. Cool down to 30°C.
7. Add 1.0 kg of item 15 (70°C) to a suitable vessel and heat to 85° to 90°C for 1 hour.
8. Cool to 20° to 25°C.
9. Mix items 13 and 4 and immediately add to item 15 (20° to 25°C) in the storage vessel.
10. Mix for 2 minutes. Store in a previously cleaned storage vessel.
11. Load item 2 and 100.0 g of item 15 (25° to 30°C) in a stainless steel mixing vessel with lid and stirrer.
12. Mix for 5 minutes at medium speed.
13. Transfer by vacuum into mixer. Load 80.0 g of item 1 and 80.0 g of item 15 (25° to 30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
14. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
15. Load 80.0 g of item 1 and 80.0 g of item 15 (25° to 30°C) from step above in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
16. Load 80.0 g of item 1 and 80.0 g of item 15 (25° to 30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
17. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Load 50.0 g of item 1 and 50.0 g of item 15 (25° to 30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
18. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Transfer item 11 into mixer by vacuum.
19. Dissolve item 10 in 2.0 g of item 15 (25° to 30°C) and transfer into mixer. Mix and homogenize for 30 minutes at 1420 rpm, under vacuum 0.5 bar.
20. Dissolve items 5 and 7 in item 9 (50° to 60°C) by stirring in stainless steel container in a water bath.
21. Dissolve items 8 and 6 and add it to parabens-glycol solution.
22. Mix well; add to mixer. Mix and homogenize for 10 minutes under vacuum 0.5 bars.
23. Mix items 12, 3, and 2.0 g of item 15 and immediately add to the mixer. Mix for 10 minutes without vacuum.

24. Add cold item 15 to make up the volume up to 1 L. Mix for 15 minutes.
25. Transfer the suspension through 630-micron sieve to the stainless steel storage tank. Final pH 7.5 to 8.0, density 1.04 to 1.06.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.00	1	Aluminum hydroxide gel	214.00
80.00	2	Magnesium hydroxide paste 30%	54.20
150.00	3	Sorbitol (70% solution)	30.00
10.00	4	Methyl paraben	2.00
1.00	5	Propyl paraben	0.20
2.00	6	Saccharin sodium	0.40
15.00	7	Magnesium aluminum silicate (Veegum HV)	3.00
0.20	8	Ammonia solution 25%	0.04
4.50	9	Sodium hypochlorite 5%	0.90
100.00	10	Propylene glycol	20.00
0.75	11	Lemon-mint flavor	0.15
—	12	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

See above for details.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.0	1	Purified Bentonite (Veegum HS)	5.0
2.0	2	Xanthan Gum (Rhodigel)	2.0
401.0	3	Water	401.0
200.00	4	Sorbitol 70%	200.00
360.00	5	Aluminum Hydroxide Gel	360.00
320.00	6	Magnesium Hydroxide	320.00
q.s.	7	Preservative, Flavor	q.s.

MANUFACTURING DIRECTIONS

1. Add a dry blend of items 1 and 2 to item 3 slowly, agitating with maximum available shear until a smooth and uniform mix is obtained.
2. Mix together items 4 to 6 in another vessel until uniform and then add to the above mix and agitate until uniform.
3. Add item 7 and mix until uniform.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40	1	Aluminum hydroxide	40
40	2	Magnesium hydroxide	40
50 g	3	Cremophor RH 40	50
1.0	4	Silicon oil DC 200 (Serva)	1.0
100	5	Kollidon CL-M	100
q.s.	6	Water	76.9

MANUFACTURING DIRECTIONS

1. Mix Cremophor RH 40 well with the silicon oil.
2. Add the water and suspend the solid substances.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.00	1	Magnesium aluminum silicate (Magnabrite S) 5% suspension	200.00
2.0	2	Methylparaben	2.0
1.0	3	Propylparaben	1.0
0.50	4	Saccharin sodium	0.50
500.00	5	Aluminum hydroxide-magnesium hydroxide fluid gel	500.00
3.0	6	Polysorbate 80	3.0
2.0	7	Flavor	2.0
291.5	8	Water, purified	291.5

MANUFACTURING DIRECTIONS

1. Add the parabens and saccharin to item 1 with stirring until dissolved (may heat to 80°C to dissolve).
2. Add item 5 with mixing. Finally, add items 6 and 7.
3. Mix well.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
215.00	1	Aluminum hydroxide gel	217.00
80.00	2	Magnesium hydroxide paste 30%	56.00
25.00	3	Simethicone emulsion (simethicone antifoam M30)	18.50
150.00	4	Sorbitol (70% solution)	30.00
0.20	5	Ammonia solution 25%	0.04
10.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	0.20
28.00	8	Methylcellulose 4000 (Methocel A4M)	5.60
2.00	9	Saccharin sodium	0.40
4.50	10	Sodium hypochlorite 5%	0.90
1.00	11	Lemon-mint flavor	0.20
—	12	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

See above for directions.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
27.0	1	Simethicone 30%	27.0
30.0	2	Cremophor RH 40	30.0
70.0	3	Water	70.0
80.0	4	Aluminum hydroxide dry gel (Giulini)	80.0
80.0	5	Magnesium hydroxide	80.0
90.0	6	Kollidon CL-M	90.0
100.00	7	Sorbitol, crystalline	100.00
4.0	8	Banana flavor	4.0
5.00	9	Coconut flavor	5.00
1.00	10	Saccharin sodium	1.00
q.s.	11	Water	q.s. to 1 L
q.s.	12	Citric acid to adjust pH to 9.0	q.s.

MANUFACTURING DIRECTIONS

1. Mix Cremophor RH 40 with simethicone, heat to about 50°C, stirring well.
2. Add the warm water.
3. Dissolve the flavors and saccharin in water and suspend aluminum hydroxide, magnesium hydroxide and Kollidon CL-M.
4. Add emulsion of items 1 to 3 to the stirred suspension of items 4 to 11 and adjust pH to about 9 with item 12 if needed.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200/00	2	Basic Magnesium carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol, crystalline	211.50
41.3	5	Orange flavor	41.3
82.6	6	Kollidon 30	82.6
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

MANUFACTURING DIRECTIONS

1. Granulate mixture of items 1 to 5 with solution of items 6 to 10.
2. Pass through a sieve and dry.
3. Shake 58 g of the granules with 100 mL of water. Homogenize.

Aminacrine Hydrochloride Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Aminacrine hydrochloride	1.00
60.00	2	Thymol	60.00
100.00	3	Glyceryl monostearate	100.00
30.00	4	Cetostearyl alcohol	30.00
20.00	5	Polyoxyl 40 stearate	20.00
100.00	6	Liquid paraffin	100.00
5.00	7	Cetrimide	5.00
1.50	8	Isopropyl alcohol	1.50
q.s.	9	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 6 in a suitable stainless steel vessel and add and dissolve item 1 by heating to 65°C.
2. Charge items 3 to 5, 7, and 9 in a separate vessel and mix.
3. Add above items to step 1.
4. On cooling, add items 8 and 2 and mix.
5. Fill.

Aminolevulinic Acid HCl for Topical Solution, 20%

Aminolevulinic acid HCl for topical solution, 20%, contains the hydrochloride salt of aminolevulinic acid, an endogenous 5-carbon aminoketone. The stick for topical application is a two-component system consisting of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle comprising alcohol (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of aminolevulinic acid hydrochloride as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. The 20% topical solution is prepared just before the time of use by breaking the ampules and mixing the contents by shaking the stick applicator.

Amoxacillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)[a]	**Item**	**Material Name**	**Quantity/5 L (g)**
125.00	1	Amoxacillin, USE amoxacillin trihydrate, 8% excess	143.50
1.04	2	Simethicone A	1.04
111.11	3	Castor sugar	111.11
444.44	4	Castor sugar	444.44
2479.86	5	Castor sugar	2479.86
23.33	6	Sodium citrate	23.33
1.67	7	Xanthan gum	1.67
13.33	8	Blood orange dry flavor	13.33
0.74	9	Vanilla dry flavor	0.74
4.44	10	Orange banana dry flavor	4.44
14.44	11	Aerosil 200	14.44

[a]After reconstitution

MANUFACTURING DIRECTIONS

1. Charge items 3 and 2 in a mixer and mix for 2 minutes.
2. Add item 4 and items 6 to 11 and mix for 5 minutes.
3. Pass through Fitz Mill, impact forward at high speed using sieve 24228.
4. In a separate mixer, charge items 5 and 1 and mix well, passing through a sifter.
5. Add to step 3 and mix for 20 minutes.
6. Fill 65.00 g for 100 mL and 39 g for 60-mL pack size.

Amoxacillin–Clavulanate Syrup

Bill of Materials			
Scale (g/60 mL volume)	**Item**	**Material Name**	**Quantity/kg (g)**
1.50	1	Amoxacillin (1.25 G/60 mL),[a] USE amoxacillin trihydrate	215.67
0.393	2	Potassium clavulanate (equivalent to clavulanic acid 0.312 g)	56.59
0.15	3	Xanthan gum	21.56
1.80	4	Hydroxy propyl methyl cellulose	258.80
0.15	5	Saccharin sodium	21.56
0.30	6	Colloidal silica	43.13
0.01	7	Succinic acid	1.44
1.50	8	Silica gel	215.67
0.18	9	Peach dry flavor	26.39
0.23	10	Strawberry dry flavor	33.99
0.73	11	Lemon dry flavor	105.16

[a]6.955 g/60 mL: 156 mg/5 mL syrup 60 mL (125 mg amoxacillin and 31.25 mg clavulanic acid).

MANUFACTURING DIRECTIONS

Throughout the process of manufacturing and filling, maintain relative humidity of not more than (NMT) 40%.

1. Mill 50% of amoxacillin trihydrate, Saccharin sodium (dried to NMT 2% moisture by Karl Fischer method), and succinic acid through a #100 mesh sieve using Fitzmill or equivalent with blades forward.
2. Transfer to a blending mixer and mix for 15 minutes.
3. Mill remaining amoxacillin trihydrate through a #100 mesh using Fitzmill or equivalent and mix with above screened powders; mix for 15 minutes.
4. Mill xantham gum, hydroxypropyl methylcellulose (dried to NMT 2% mositure dried at 105°C for 2 hours), colloidal silica, and silica gel through a #100 screen using Fitzmill or equivalent with knives forward. Add to above mixture in step 2 and mix for 15 minutes at medium speed.
5. Screen all dry flavors through a #100 mesh screen and add to above mixture.
6. Fill dry powder about 7 g in dry 60-mL glass bottles at a fill weight based on the assay of the active constituent.

Bill of Materials		
Scale (mg/5 mL)	**Item**	**Material Name**
400.00	1	Amoxacillin as trihydrate
57.00	2	Clavulanic acid as potassium salt
2.69	3	Citric acid
8.33	4	Sodium citrate
28.10	5	Microcrystalline cellulose and sodium sodium carboxymethylcellulose
10.00	6	Xanthan gum
16.67	7	Colloidal silicon dioxide
216.60	8	Silicon dioxide
13.30	9	Strawberrry flavor
15.00	10	Caramel flavor
6.70	11	Saccharin sodium
q.s.	12	Cellulose microcrystalline[a]

[a]Total amount filled per bottle to deliver 12 doses is 15 g for 400 and 600 mg label of amoxacillin; For 200 mg and 300 mg amoxicillin label, the total fill weight is 12 g; adjust using item 12. Use method above to manufacture the final product.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/5 L (g)**
125.00	1	Ampicillin, USE ampicillin trihydrate, 8% excess	144.25
1.00	2	Simethicone A	1.00
138.90	3	Castor sugar	138.90
27.44	4	Sodium citrate	27.44
7.00	5	Xanthan gum	7.00
15.00	6	Blood orange dry flavor	15.00
0.78	7	Vanilla dry flavor	0.78
7.55	8	Strawberry dry flavor	7.55
10.00	9	Aerosil 200	10.00
138.90	10	Castor sugar	138.90
2747.90	11	Castor sugar	2747.90

MANUFACTURING DIRECTIONS

1. All operations to be completed in relative humidity 45 to 55% and temperature 23˚ to 25˚C.
2. Charge items 2 and 3 in a suitable blender and mix for 5 minutes.
3. Charge in a separate mixer, items 1, 4 to 10 and mix for 5 minutes.
4. Add step 2 into step 3 and mix for 10 minutes.
5. Add item 11 and mix for 10 minutes.
6. Fill 65 g for 100-mL pack and 39 g for 60-mL pack. For 250-mg strength, adjust active ingredient and adjust with item 11.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/G)	**Item**	**Material Name**	**Quantity/Kg (g)**
50.00	1	Ampicillin trihydrate	50.00
50.00	2	Sodium citrate	50.00
21.00	3	Citric acid crystalline	21.00
50.00	4	Sodium gluconate	50.00
400.00	5	Sorbitol crystalline	400.00
60.00	6	Kollidon CL-M	60.00
15.00	7	Orange flavor	15.00
5.00	8	Lemon flavor	5.00
4.00	9	Saccharin sodium	4.00

MANUFACTURING DIRECTIONS

1. Mix all components and fill appropriate amount.

Ampicillin and Cloxacillin Oily Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
15.00	1	Ampicillin sodium	15.00
40.00	2	Cloxacillin sodium	40.00
30.00	3	Lutrol F 68	30.00
q.s.	4	Antioxidant	q.s.
915.00	5	Castor oil	915.00

MANUFACTURING DIRECTIONS

1. Charge items 4 and 5 in a suitable stainless steel jacketed vessel; heat to 50˚C. Do not overheat, as castor oil may decompose.
2. Add and dissolve item 3.
3. Add and dissolve items 1 and 2.
4. Homogenize and fill.

Amprenavir Capsules

Amprenavir is an inhibitor of the human immunodeficiency virus (HIV) protease. The chemical name of amprenavir is (3 S)-tetrahydro-3-furyl N-[(1 S,2 R)-3-(4-amino-N-isobutylbenzenesulfonamido)-1-benzyl-2-hydroxypropyl]carbamate. Amprenavir is a single stereoisomer with the (3 S)(1 S,2 R) configuration. It has a molecular formula of C 25 H 35 N 3 O 6 S. The capsules are available for oral administration in strengths of 50 and 150 mg. Each 50-mg capsule contains the inactive ingredients D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol 19 mg. Each 150-mg capsule contains the inactive ingredients TPGS, PEG 400 740 mg, and propylene glycol 57 mg. The capsule shell contains the inactive ingredients D-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink. Each 150-mg capsule contains 109 U vitamin E in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose is 1744 U.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
150.00	1	Amprenavir	150.00
400.00	2	D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS)	400.00
200.50	3	Polyethylene glycol 400	200.50
39.40	4	Polyethylene glycol 400	39.50

MANUFACTURING DIRECTIONS

1. Charge item 2 in a suitable stainless steel-jacketed vessel and heat to 50˚C until liquefied.
2. Add item 3 (90%) at 50˚C and mix until homogenous solution obtained.
3. Increase temperature to 65˚C, add item 1, and stir to dissolve.
4. Add item 4 and balance of item 2, cool to room temperature, apply vacuum to remove air entrapped.
5. Fill in size-12 oblong, white opaque soft gelatin capsules using a capsule-filling machine.
6. Dry the capsule shells to moisture of 3 to 6% water and a shell hardness of 7 to 10 Newtons, and pack in a suitable container.

Amprenavir Oral Solution

One milliliter (1 mL) of AGENERASE Oral Solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubblegum flavor, citric acid (anhydrous), D-alpha tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each milliliter of AGENERASE oral solution contains 46 U vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir. The recommended daily dose of AGENERASE oral solution of 22.5 mg/kg twice daily corresponds to a propylene glycol intake of 1650 mg/kg per day.

Anise Oil Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Anise oil	10.00
17.00	2	Cremophor RH 40	17.00
340.00	3	Ethanol	340.00
q.s.	4	Preservatives	q.s.
633.00	5	Water	633.00

MANUFACTURING DIRECTIONS

1. Mix the anise oil with Cremophor RH 40, heat to about 65°C.
2. Stir vigorously and slowly add the hot solution of items 3 to 5. Clear or slightly opalescent, colorless liquid.

Antipyrine and Benzocaine Elixir

Each milliliter contains antipyrine 54.0 mg, benzocaine 14.0 mg, and glycerin anhydrous q.s. to volume (also contains oxyquinoline sulfate).

Apraclonidine Hydrochloride Ophthalmic Solution

Each milliliter of IOPIDINE® 0.5% ophthalmic solution contains apraclonidine hydrochloride 5.75 mg equivalent to apraclonidine base 5 mg; benzalkonium chloride 0.01%. sodium chloride, sodium acetate, sodium hydroxide or hydrochloric acid (pH 4.4 to 7.8), and purified water.

Ascorbic Acid Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.00	1	Ascorbic acid	100.00
q.s.	2	Propylene glycol	q.s. to 1 L

MANUFACTURING DIRECTIONS

Keep under CO_2 protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only. Propylene glycol must be water white.

1. Load 86.8 g propylene glycol into a glass-lined or suitable stainless steel-jacketed tank.
2. While mixing, heat to 70° to 80°C.
3. Bubble CO_2 gas into the propylene glycol from the bottom of the tank.
4. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO_2 protection.
5. When the ascorbic acid is in solution, immediately cool to approximately 25°C while continuing to mix. Also, while cooling, change CO_2 addition from tank bottom to tank top.
6. q.s. to 1 L, using propylene glycol and mix for at least 10 minutes.
7. Use a prefilter pad and a lint-free filter paper, E&D No. 950 or its equivalent; alternatively, a Sparkler filter (or equivalent) may be used.
8. Recirculate the product through the filter press until sparkling clear.
9. Flush a suitable storage tank with CO_2 gas and continue CO_2 gas protection while product is being collected.
10. Filter the product into the storage tank and hold under CO_2 protection.
11. Flush headspace of storage tank with CO_2 gas protection.

Atovaquone Suspension

MEPRON suspension is a formulation of microfine particles of atovaquone. The atovaquone particles, reduced in size to facilitate absorption, are significantly smaller than those in the previously marketed tablet formulation. MEPRON suspension is for oral administration and is bright yellow with a citrus flavor. Each teaspoonful (5 mL) contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
150.00	1	Atovaquone microflulidized[a]	150.00
5.00	2	Poloxamer 188	5.00
10.00	3	Benzyl alcohol	10.00
q.s.	4	Water, purified	q.s. to 1 L

[a]Preparation of microfluidized particles of atovaquone: 600 mL of a mixture consisting of 2.5% w/v atovaquone in 0.25% w/v aqueous Celacol M2500 and passed through fluidizer such as model 120B Microfluidizer connected to a 90-psi pneumatic supply and adjusted to produce a fluid pressure of 15,000 psi. Recirculate continuously through the interaction chamber for at least 45 minutes (65 to 77 passes) to achieve particle size less than 3 microns.

MANUFACTURING DIRECTIONS

1. Charge items 4 and 3 in a suitable stainless steel vessel and mix well.
2. Add and mix item 2 with gentle mixing.
3. Add gradually item 1 and mix; pass through homogenizer.

Azelastine Hydrochloride Nasal Spray

Astelin nasal spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Azelastine hydrochloride	1.00
0.50	2	Edetic acid disodium dehydrate	0.50
6.80	3	Sodium chloride	6.80
0.125	4	Benzalkonium chloride	0.125
0.44	5	Citric acid	0.44
6.48	6	Sodium monohydrogen phosphase. 12 H_2O	6.48
1.0	7	Hydroxypropyl methyl cellulose Methocel E4M	1.00
q.s.	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 90% of item 8 in a suitable stainless steel vessel.
2. Dissolve in the following order: azelastine hydrochloride, edetic acid, sodium chloride, benzalkonium chloride, citric acid, and sodium monohydrogen-phosphate, and mix well.
3. Bring to volume with item 8.
4. Pass the solution through a membrane filter of pore size 0.22 microns.
5. The filtrate has a pH value of 6.8 ± 0.3.
6. Fill in plastic bottles that are closed with a conventional spray insert or into plastic or glass bottles that are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example, used that spray about 0.14 mL of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride is sprayed into the nose per actuation in the form of the solution.

Azithromycin Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.00	1	Azithromycin, USE azithromycin dehydrate	69.30
4.41	2	Sucrose	883.00
0.065	3	Sodium Phosphate 12 hydrate	13.00
0.0075	4	Xanthan gum	1.50
0.02	5	Sodium cyclamate	4.00
0.02	6	Sodium sacchrin	2.00
0.025	7	Glycamil	5.00
0.50	8	Starch pregelatinized	100.00
0.02	9	Flavor	4.00
0.055	10	Flavor	11.00
0.04	11	Flavor	8.00
0.75	12	Sorbitol 70%	150.00
0.75	13	Propylene glycol	140.00
0.0075	14	Methyl paraben	1.50
0.0015	15	Propyl paraben	0.30
q.s.	16	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge in a suitable stainless steel double-cone blender, sucrose, sodium phosphate, xanthan gum, sodium cyclamate, sodium saccharin, glycamil, and starch pregelatinized.
2. Mix for 15 minutes.
3. Mill the mixture in step 2 using a hammer mill (hammer forward) equipped with a 2-mm screen at high speed.
4. Charge into a double-cone mixer the mixture from step 3 and add azithromycin and flavors.
5. Mix for 15 minutes.
6. Fill 11.01 g per bottle. The bottle must be reconstituted with 10 mL of the diluent (see step below) to obtain 16.5 mL of suspension with concentration of 200 mg/5 mL.
7. Prepare the diluent by first dissolving items 14 and 15 in item 13 at 69° to 70°C, then mix with item 12 and item 16.

Azithromycin Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Azithromycin dihydrate	50.00
50.00	2	Sodium citrate	50.00
20.00	3	Citric acid	20.00
600.00	4	Sucrose	600.00
90.00	5	Kollidon CL-M	90.00
5.00	6	Cremophor RH 40	5.00
2.00	7	Chocolate flavor	2.00
100.00	8	Water, purified	100.00
q.s.	9	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 to 5 in a suitable mixing vessel and mix.
2. In a separate vessel add and mix items 6 to 8 and add to step 1. Mix.
3. Bring to volume. Homogenize and fill.

Azulene Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Azulene	10.00
30.00	2	Cremophor RF 40	30.00
q.s.	3	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable mixing vessel and heat to 60˚C.
2. In a separate vessel, heat item 3 to 60˚C and then add to step 1. Mix well for a clear solution.

Barium Sulfate Oral Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
230.00	1	Barium sulfate	230.00
11.50	2	Kollidon 90F	11.50
0.92	3	Carboxymethylcellulose sodium	0.92
0.70	4	Sodium bisulfite	0.70
q.s.	5	Preservatives	q.s.
q.s.	6	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 90% of item 6 in a suitable jacketed vessel.
2. Add and mix preservatives and item 3. Mix well. Allow to hydrate.
3. Add item 2 and mix well until clear solution is obtained.
4. Add item 1 and mix to a smooth suspension. Homogenize if necessary.

Beclomethasone Dipropionate Inhalation Aerosol

The active component of inhalation aerosol is beclomethasone dipropionate, an anti-inflammatory corticosteroid having the chemical name 9-chloro-11(beta),17,21-trihydroxy-16(beta)-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate. It is a pressurized, metered-dose aerosol intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. The 40-mcg strength delivers 40 mcg of beclomethasone dipropionate from the actuator and 50 mcg from the valve. The 80-mcg strength delivers 80 mcg of beclomethasone dipropionate from the actuator and 100 mcg from the valve. It is a metered-dose, manual-pump spray unit containing a suspension of beclomethasone dipropionate, monohydrate equivalent to 0.084% w/w beclomethasone dipropionate in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and phenylethyl alcohol. The suspension is formulated at a target pH of 6.4, with a range of 5.5 to 6.8 over its shelf life.

Bill of Materials			
Scale (mcg/mg)	**Item**	**Material Name**	**Quantity/Kg (g)**
1.60	1	Beclomethasone dipropionate	1.60
35.20	2	Ethanol	35.20
0.16	3	Oleic acid	0.16
960.00	4	HFA 227	960.00

MANUFACTURING DIRECTIONS:

1. Charge beclomethasone dipropionate into a pressure addition vessel and dissolve with stirring in ethanol in which oleic acid has been previously dissolved.
2. After sealing and evacuation of step 1, add item 4, which has previously been aerated with carbon dioxide and adjusted to a pressure of 6.5 bar (20˚C), in another pressure vessel, with stirring. The solution obtained is dispensed into aluminum containers sealed with metered valves by means of the pressure-filling technique (e.g., units from Pamasol W. Maeder, Pfaffikon, Switzerland).

Beclomethasone Dipropionate and Salbutamol Sulfate Nasal Spray

Dissolve 15.6 g of beclomethasone dipropionate in 811 g of ethanol, which contains 3 g of oleic acid. The clear solution is mixed with 7.3 kg of HFA 227. The mixture obtained is added to 9.4 g of initially introduced salbutamol sulfate and adequately homogenized. After conclusion of the homogenization, the mixture is diluted with 2 kg of HFA 227 that have been aerated with carbon dioxide and adjusted to a pressure of 5 bar (20˚C), diluted, and finally homogenized. The finished preparation is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Benzethonium Chloride Solution

Benzethonium chloride 1%, water, amphoteric 2, aloe vera gel, DMDM hydantoin, citric acid.

Benzethonium Chloride and Benzocaine Topical Anesthetic

Benzethonium chloride 0.2%, benzocaine 20%; inactive ingredients: acetulan, aloe vera oil, menthol, methyl paraben, N-butane/P152a (65:35), PEG 400, monolaurate, polysorbate 85.

Benzocaine and Tetracaine Topical Solution

Bill of Materials			
Scale (g/100 mL)	**Item**	**Material Name**	**Quantity/L (g)**
14.00	1	Benzocaine	140.00
2.00	2	Butyl Aminobenzoate	20.00
2.00	3	Tetracaine Hydrochloride	20.00
0.50	4	Benzalkonium Chloride	5.00
0.005	5	Cetyl Dimethyl Ethyl Ammonium Bromide	0.05
q.s.	6	Water, purified	q.s. to 1 L

Benzyl Benzoate Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.00	1	Benzyl benzoate	100.00
220.00	2	Cremophor RH 40	220.00
410.00	3	Ethanol 96%	410.00
270.00	4	Water	270.00

MANUFACTURING DIRECTIONS

1. Heat the mixture of benzyl benzoate and Cremophor RH 40 to about 60˚C.
2. Stir strongly and slowly add the water. Finally add the ethanol. This produces a clear, colorless liquid.

Beta-Estradiol Vaginal Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (Pluronic P105 45%, propylene glycol 48%, water 7%)	q.s. to 1 L
0.10	2	Beta-estradiol	0.10
q.s.	3	Perfumes	q.s.

MANUFACTURING DIRECTIONS

1. Add the beta estradiol and propylene glycol into a clean vessel.
2. Subsequently add the poloxamer and water to the vessel.
3. Mix until uniform.

Betamethasone Syrup

Celestone syrup contains 0.6 mg betamethasone in each 5 mL. The inactive ingredients for celestone syrup include alcohol; cellulose, powdered; citric acid, anhydrous; FD&C red no. 40; FD&C yellow no. 6; flavor cherry artificial 13506457 IFF; flavor orange natural terpeneless 73502530 IFF; propylene glycol; sodium benzoate; sodium chloride; sorbitol solution; sugar, granulated; and water, purified.

Bismuth Carbonate Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
266.66	1	Light kaolin	266.66
8.30	2	Pectin	8.30
6.70	3	Bismuth carbonate	6.70
9.40	4	Microcrystalline cellulose avicel RC-591	9.40
1.40	5	Methylparaben	1.40
0.20	6	Saccharin sodium	0.20
0.40	7	Aspartame	0.40
40.00 mL	8	Sorbitol	40.00 mL
5.00 mL	9	Ethanol	5.00 mL
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve item 2 in hot water. Disperse item 1 in 75 mL room-temperature item 10.
2. With constant agitation, add item 3 and continue stirring.
3. Mix and cool to room temperature.
4. Disperse item 4 in item 10. Add it to the batch. Dissolve item 2 in item 1 dispersion and add to batch.
5. Dissolve items 6 and 7 in water and add. Add flavor, color, and water to volume.
6. Pass through homogenizer or colloid mill if necessary.

Bismuth Subsalicylate Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
15.00	1	Magnesium aluminum silicate (Magnabrite K)	15.00
1.50	2	Methylcellulose	1.50
910.00	3	Water, purified	910.00
0.50	4	Saccharin sodium	0.50
30.00	5	Bismuth subsalicylate	30.00
4.00	6	Salicylic acid	4.00
10.00	7	Sodium salicylate	10.00
29.00	8	Ethanol	29.00
q.s.	9	Preservatives	q.s.
q.s.	10	Colorings	q.s.

MANUFACTURING DIRECTIONS

1. Dry blend items 1 and 2 and add them to item 3 slowly, agitating until smooth.
2. Add items 4 to 7 to this dispersion gradually, mixing well each time.
3. Add items 8 to 10 to smooth mix.

Bromazepam Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.50	1	Bromazepam	2.50
5.00	2	Saccharin sodium	5.00
0.10	3	Sequestrene disodium	0.10
5.00	4	Flavor	5.00
25.00	5	Flavor	25.00
q.s.	6	Sodium hydroxide for pH adjustment	q.s.
50.00	7	Water purified	50.00
q.s.	8	Propylene glycol	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 8 in a suitable stainless steel mixing vessel and, while stirring, add item 3 and dissolve.
2. Add item 7 and stir continuously. Add item 2 and then item 1 and stir to dissolve.
3. Add flavors and mix.
4. Check and adjust pH to 5.0, if necessary, using item 5.
5. Make up volume with item 8.

Bromhexine Hydrochloride Syrup — Alcohol Free

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
4.000	1	Bromhexine HCl	0.800
1000.000	2	Glycerin (glycerol)	200.000
12.000	3	Sodium benzoate	2.400
1.700	4	All fruit flavor	0.340
17.000	5	Tartaric acid	3.400
2250.000	6	Sorbitol (70% solution)	450.000
10.000	7	Carboxymethylcellulose sodium (Sodium CMC)	2.000
q.s.	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 240.0 g of item 8 (25˚C) to the manufacturing vessel.
2. Add item 5 and mix for 20 minutes at high speed. Unload 180.0 g of item 2 to the manufacturing vessel and mix for 3 minutes.
3. Add item 1 to the manufacturing vessel and mix for 30 minutes at high speed.
4. Add 20.0 g of item 2 in a suitable vessel and levigate item 7 using stirrer, carefully avoiding lump formation.
5. Add 40.0 g of item 8 (70˚C) to the stainless steel container while mixing to make a clear mucilage; mix for 15 minutes. Avoid air entrapment.
6. Cool down to 25˚ to 30˚C while mixing at slow speed.
7. Transfer the mucilage to the manufacturing vessel. Rinse the vessel with 10.0 g of item 8 and transfer to the manufacturing vessel.
8. Mix at slow speed for 20 minutes. Transfer item 6 to the manufacturing vessel while mixing. Mix at low speed for 5 minutes.
9. Add 20.0 g of item 8 (25˚C) in a separate stainless steel container and dissolve item 3 using Ekato stirrer until clear solution is obtained.
10. Transfer this solution to the manufacturing vessel and mix at low speed for 3 minutes. Add item 4 to the manufacturing vessel and mix at low speed for 3 minutes.
11. Check and record the pH of the solution. Limit: 3.3 to 3.7. Adjust the pH of the solution with 10% solution of sodium hydroxide if required.
12. Make the volume up to 1 L with item 8 (25˚C) and finally mix for 15 to 20 minutes at high speed.
13. Filter the syrup at 1.5 bar. Recirculate.

Bromhexine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
4.00	1	Bromhexine HCl	0.80
1000000	2	Glycerin (glycerol)	200.00
10.00	3	Benzoic acid	2.00
1.00	4	All fruits flavor	0.34
5000	5	Tartaric acid	1.00
151.50	6	Alcohol (ethanol 95%)	30.31
2857000	7	Sorbitol (70% solution)	571.40
10.00	8	Carboxymethylcellulose sodium (sodium CMC)	2.00
0.70	9	Sodium hydroxide pellets	0.14
q.s.	10	Water, purified,	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 250.0 g of item 10 to a suitable stainless steel manufacturing vessel and heat to 65° to 70°C.
2. Add 20.0 g of item 2 in a separate stainless steel container and mix item 8 using Ekato stirrer, carefully avoiding lump formation.
3. Transfer the slurry to the manufacturing vessel while continuing to mix to make a clear mucilage. Avoid air entrapment.
4. Cool down to 30°C while mixing at slow speed.
5. Transfer the mucilage to container. Load 100.0 g of item 2 to the manufacturing vessel.
6. Add item 6 in a separate stainless steel container and dissolve item 3 using stirrer.
7. Add 60.0 g of item 2 to the container while mixing at slow speed.
8. Add and dissolve item 1 to the container while mixing at slow speed. Avoid splashing of the solution. Check that bromhexine is dissolved completely.
9. Add item 4 to the container and mix well. Transfer the solution to the manufacturing vessel while mixing at high speed.
10. Rinse the container with 20.0 g of item 2 and transfer the rinsing to the manufacturing vessel while mixing.
11. Rinse the container with 20.0 g of item 10 and transfer the rinsing to the manufacturing vessel while mixing. Add 15.0 g of item 10 in a separate stainless steel container and dissolve item 5 using stirrer and transfer to the manufacturing vessel while mixing.
12. Check clarity of the solution in manufacturing vessel. The solution must be clear without any undissolved particles of the drug.
13. Add item 7 to the manufacturing vessel while mixing at high speed.
14. Transfer the cooled mucilage of item 8 to the manufacturing vessel used above while mixing at slow speed.
15. Check and record the pH of the solution (limit 3.3 to 3.6).
16. Dissolve item 9 in 5.0 g of cooled item 10 (30°C) in a separate stainless steel container.
17. Adjust the pH of the syrup in manufacturing vessel using the sodium hydroxide solution. Add sodium hydroxide solution in small portions at a time. Mix well and check the pH after every addition. Adjust the pH to 3.5 (limit 3.3 to 3.6).
18. Make up the volume up to 1.0 L with item 10 and, finally, mix for 15 to 20 minutes at high speed. Check and record the pH (limit 3.3 to 3.6). Filter the syrup at 1.5 bar. Recirculate.

Budesonide Inhaler

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
20.00	1	Budesonide	20.00
1190.00	2	Oleic Acid	1190.00
1372.00	3	Trichloromonofluoromethane (Propellant 11)	1372.00
2745.00	4	Dichlorodifluoremethane (Propellant 12)	2745.0
1373.00	5	Dichlorotetrafluoroethane (Propellant 114)	1373.00

MANUFACTURING DIRECTIONS

1. Mix oleic acid in trichloromonofluoromethane in a suitable mixer.
2. Suspend budesonide in step 1 while mixing. Homogenize for 10 minutes.
3. On quality control release, fill the suspension, 2.582 g in aluminum containers.
4. Crimp the valve and pressurize with the mixture of dichlorodifluoromethane and dichlorotetrafluoromethane, 4.118 g per container.

Butamirate Citrate Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/5L (g)**
4.00	1	Butamirate citrate	4.00
12.50	2	Citric acid monohydrate	12.50
1750.00	3	Sorbitol	1750.00
1250.00	4	Glycerin	1250.00
6.25	5	Saccharin sodium	6.25
5.00	6	Sodium benzoate	5.00
10.00	7	Lemon flavor	10.00
q.s.	8	Sodium hydroxide	2.50
q.s.	9	Water purified q.s. to	5 L

MANUFACTURING DIRECTIONS

1. Dissolve items 2 to 4 in item 9 (90%).
2. Add and dissolve item 1.
3. Add items 5 to 7.
4. Add item 8.
5. Bring to volume.

Caffeine Citrate Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Caffeine, USE caffeine citrate	20.00
5.00	2	Citric acid monohydrate	5.00
8.30	3	Sodium citrate monohydrate	8.30
q.s.	4	Water purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve item 1 in a solution of items 2 and 3 in item 4.
2. Adjust pH to 4.7

Calcipotriene Solution

Dovonex® (calcipotriene solution) scalp solution 0.005%, is a colorless topical solution containing 0.005% calcipotriene in a vehicle of isopropanol (51% v/v) propylene glycol, hydroxypropyl cellulose, sodium citrate menthol, and water.

Calcitonin Nasal Spray

Calcitonin-salmon, 2200 U per mL (corresponding to 200 U per 0.09 mL actuation), sodium chloride, benzalkonium chloride, nitrogen, hydrochloric acid (added as necessary to adjust pH), and purified water.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.1375	1	Salmon calcitonin, 10% excess	0.152
7.50	2	Sodium chloride	7.50
0.10	3	Benzalkonium chloride	0.10
q.s.	4	Hydrochloric acid (1 N) to adjust pH	q.s.
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 (90%), 2, and 3 in a suitable stainless steel mixing vessel under protection of nitrogen gas and mix well.
2. Measure and adjust pH to 3.7 using item 4.
3. Filter through 0.20-micron filter.
4. Add balance of item 1 in item 5 to step 3. Mix.
5. Fill into a spray nasal dispenser with a solution volume of 2 mL. The composition comprises approximately 550 MRC-units active ingredient per milliliter, and the applicator delivers a quantity comprising 55 units per actuation.

Calcium Carbonate and Guar Gum Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
400.00	1	Calcium carbonate	80.00
3935.00	2	Water purified	787.00
1000.00	3	Sorbitol solution (70%)	200.00
13.00	4	Xanthan gum	2.60
5.00	5	Hydroxyethyl cellulose	1.00
120.00	6	Magnesium hydroxide	24.00
25.00	7	Flavor strawberry[a]	5.00
1.425	8	Saccharin sodium	0.285
100.00	9	Guar gum	20.00

[a]Powder flavor is used; can change according to requirement.

MANUFACTURING DIRECTIONS

This is a preservative-free formula; shelf-life stability is achieved by maintaining pH of the suspension above 9.00 through the addition of magnesium hydroxide. Absence of preservatives makes it a more palatable formula but requires extra care in the manufacturing process. Rigidly control the microbial specification of all ingredients. Thoroughly clean all equipment and rinse with 1% sodium hypochlorite solution before use. Finally, rinse with purified water.

1. In a clean vessel, heat item 2 to 90˚C and maintain for 20 minutes. Cool to room temperature.
2. In about 90% of the quantity of item 2, add item 3 to step 1 and mix well. Set aside the balance of quantity of item 2 for bringing to volume the suspension in the step 8.
3. Add by sprinkling items 3, 4, and 9, gradually mixing aggressively to ensure fine dispersion; the powders may be passed through an appropriate sieve to break any lumps.
4. Mix for 30 minutes.
5. Add and mix item 1 for 15 minutes after passing through a fine mesh to break any lumps.
6. Add item 6 after passing through 100 mesh screen and mix for 15 minutes.
7. Add flavor and sweetener and stir for another 15 minutes. Bring to volume (if necessary) and mix for 10 minutes.
8. Check the pH of suspension to 9.00 and above. Add small quantity of magnesium hydroxide if needed to bring pH to above 9.0.
9. Heat the suspension in a covered container for 30 minutes at 68˚C (maintain 68˚C for 30 minutes); this is a pasteurizing step to reduce microbial load.
10. Fill in clean bottles tested for microbial contamination.

Calcium Iodide and Ascorbic Acid Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
311.60	1	Glucose liquid (corn syrup)	311.6
53.90	2	Glycerin (96%)	53.9
30.00	3	Calcium iodide anhydrous, USE calcium iodide solution 27% w/w	111.11
1.0	4	Ascorbic acid white powder	1.0
485.3	5	Sucrose (sugar, granulated)	485.3
0.8	6	Saccharin sodium powder[a]	0.8
8.0	7	Sodium cyclamate	8.0
1.31	8	Flavor, honey	1.31
0.33	9	Flavor, floral mint	0.33
51.53	10	Alcohol (ethanol) 190 proof	51.53
0.60	11	Isoproterenol sulfate powder	0.60
0.05	12	Dye yellow FD&C no. 5	0.05
0.25	13	Caramel acid proof	0.25
q.s.	14	Water purified approx.	344.0 mL

[a]1.2 g of saccharin to replace cyclamate, adjust balance with sucrose.

MANUFACTURING DIRECTIONS

Isoproterenol is toxic: Wear dust mask and avoid contact. Product is highly sensitive to oxidation. Manufacture under N_2 protection, protect from light and heat; all water should be boiled, cooled and gassed with nitrogen.

1. Load glucose and glycerin into a suitable mixing tank.
2. Add 187 mL water to tank with mixing. Begin bubbling N_2 protection for the balance of the process.
3. Add and dissolve saccharin sodium and sodium cyclamate if used with mixing.
4. Add calcium iodide to the tank with good mixing. Add and dissolve ascorbic acid and sugar.
5. Dissolve the flavors in alcohol; add with mixing to the main batch. Dissolve isoproterenol in 10 to 13 mL of water and add, with mixing, to the main batch.
6. Dissolve dye in 3.5 mL purified water and add solution to tank with mixing. Dye may be deleted.
7. Add caramel with mixing to main batch. Move N_2 source bottom to top of tank. Turn off mixer. Allow to stand overnight under N_2 protection to let entrapped gases escape.
8. Bring to volume. Mix for 1 hour.
9. Filter and circulate product through a suitable filter press until sparkling clear.

Carnitine and Coenzyme Q Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Coenzyme Q 10	1.00
1.00	2	Lutrol E 400	1.00
4.00	3	Cremophor RH 40	4.00
q.s.	4	Preservative	q.s.
q.s.	5	Water	q.s. to 1 L
40.00	6	Carnitine	40.0

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1 to 5 to 60°C, stir well.
2. Add and dissolve item 6 after cooling to room temperature.

Cefaclor Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
250.00	1	Cefaclor	50.00
5.00	2	Emulsion silicone 30%	1.00
7.50	3	Xanthan gum	1.50
10.00	4	Starch Modified	2.00
4.00	5	Erythrosine aluminum lake	0.80
20.00	6	Flavor	4.00
0.75	7	Sodium lauryl sulfate	0.15
3.00	8	Methylcellulose	0.60
2960.00	9	Sucrose	592.00

For 125 mg dose, adjust with sucrose the final quantity.

Cefadroxil Monohydrate Oral Suspension

DURICEF for oral suspension contains the following inactive ingredients: FD&C yellow no. 6, flavors (natural and artificial), polysorbate 80, sodium benzoate, sucrose, and xanthan gum.

Cefpodoxime Proxetil Oral Suspension

Each 5 mL of VANTIN oral suspension contains cefpodoxime proxetil equivalent to 50 mg or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole, carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/Kg (g)**
100.00	1	Cefpodoxime paroxetil	123.50
563.75	2	Sucrose	563.50
290.00	3	D-Mannitol	290.00
1.25	4	Saccharin sodium	1.25
20.00	5	Hydroxypropyl cellulose	20.00
0.50	6	Dye yellow No. 5	0.50
1.00	7	Ethylenediamine tetraacetate disodium	1.00
q.s.	8	Orange essence	q.s.
q.s.	9	Water, purified	q.s.

MANUFACTURING DIRECTIONS

1. Charge item 1, sucrose, D-mannitol, saccharin sodium, and disodium ethylenediamine tetraacetate in an agitating granulator.
2. Granulate the mixture by agitation while spraying it with a binder of hydroxypropylcellulose and yellow no. 5 in water.
3. Pass wet mass through a 42-mesh screen in an extrusion granulator.
4. Dry the granules in a fluidized bed granulator.
5. Spray the granules with orange essence.
6. Dry granules further in the fluid bed dryer.
7. Pass granules through 30-mesh sieve and fill.

When purified water was added to the resulting dry syrup at a concentration of item 1 of 49.4 mg/mL, the dry syrup rapidly dissolved in it to give a clear orange solution.

Cefpodoxime Proxetil for Oral Suspension

Each 5 mL of VANTIN oral suspension contains cefpodoxime proxetil equivalent to 50 mg or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole, carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

CEFTIN for oral suspension, when reconstituted with water, provides the equivalent of 125 mg or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. CEFTIN for oral suspension contains the inactive ingredients polyvinyl pyrrolidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

Cefuroxime Axetil Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
25.00	1	R-cefuroxime axetil	25.00
0.40 mL	2	Sorbitol solution 70%	0.40 L
20.00	3	Saccharin	20.00
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge the sorbitol solution and 20% of item 5 in a mixing vessel.
2. Add item 1 and mix vigorously to form a suspension.
3. Add items 3 and any flavors, if needed, and mix.
4. Bring to volume.
5. Fill.

Cetrizine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	Cetrizine hydrochloride	1.03
1750.00	2	Lycosin 80/55	350.00
600.00	3	Sorbitol 70%	120.00
5.00	4	Sodium citrate	1.00
300.00	5	Propylene glycol	60.00
4.50	6	Methyl paraben	0.90
0.50	7	Propyl paraben	0.10
3.75	8	Saccharin sodium	0.75
10.00	9	Flavor raspberry	2.00
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 30% of item 10 in a stainless steel-jacketed kettle and heat to 90˚ to 95˚C.
2. Add and dissolve items 6 and 7; cool to 40˚C.
3. Add to step above item 4 and item 8 and mix to dissolve.
4. Add items 2, 3, and 5 and mix to dissolve
5. In a separate vessel, charge 30% of item 10 and add to it item 1, mix to dissolve, and then add to step 4.
6. Add flavor (or flavors) and bring to volume with item 10.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/L (g)**
0.001 mL	1	Ipecac fluid extract	1.00 mL
5.00	2	Chlophedianol hydrochloride	5.00
1.32	3	Ephedrine hydrochloride	1.32
8.8	4	Ammonium chloride	8.80
0.8	5	Carbinoxamine maleate	0.80
0.9	6	Methyl paraben	0.90
0.1	7	Propyl paraben	0.10
6.25	8	Balsam, tolu (aqueous extract)	6.25
2.66	9	Saccharin sodium powder dihydrate	2.66
319.22	10	Sucrose (sugar, granulated)	0.32
238.33	11	Glucose liquid (corn syrup)	0.24
83.933	12	Sorbitol solution 70%	0.084
40.0	13	Alcohol (ethanol)	40.00
166.67	14	Dye red	0.16
0.8	15	Flavor	0.80
100.0	16	Propylene glycol	100.00
q.s.	17	Filter aid hyflo	0.50
q.s.	18	Water purified, approx.	450.0 mL

MANUFACTURING DIRECTIONS

1. Charge balsam tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously, to mix water with balsam. Boil for half an hour and allow decanting while cooling. Discard extracted balsam tolu. Filter the supernatant liquid through filter paper and store apart.
3. Charge 150 mL water in a jacketed mixing tank; heat to boiling.
4. Add and dissolve parabens with mixing. Add and dissolve sugar with constant mixing. Heat to 70° to 75°C.
5. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium.
6. Mix well until dissolved.
7. Dissolve ammonium chloride in 28 mL water. Add to mixing tank.
8. Add extract balsam tolu with mixing.
9. Mix well and cool to 25° to 30°C. Add and dissolve epehdrine, carbinoxamine in 20 mL water and add to mixing tank. Mix well.
10. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank. Add balance of propylene glycol to mixing tank.
11. Add and dissolve Ipecac fluid extract and flavor raspberry in alcohol. Add to mixing tank. Dissolve dye in 5 mL water; add to tank with continuous mixing.
12. Rinse container with 5 mL of water and add rinsing.
13. Adjust to volume with purified water.
14. Add filter aid hyflo to syrup and mix well.
15. Recirculate through filter press or equivalent until sparkling clear.

Chloramphenicol Opthalmic Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
30.00	1	Chloramphenicol	30.00
150.00	2	Kollidon 25	150.00
q.s.	3	Preservatives	q.s.
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 90% of item 4 in a stainless steel-jacketed vessel, heat to 90˚ to 95˚C.
2. Add and dissolve preservatives.
3. Add and dissolve item 2.
4. Add and stir item 1 until a clear solution is obtained.
5. Optionally add 0.2 to 0.5% cysteine as antioxidant to prevent discoloration of item 2.

Chloramphenicol Palmitate Oral or Topical Emulsion

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
25.00	1	Chloramphenicol palmitate	25.00
40.00	2	Lutrol E 400	40.00
40.00	3	Cremophor RH 40	40.00
400.00	4	Sucrose	400.00
400.00	5	Water, purified	400.00
q.s.	6	Water, purified	q.s. to 1 L

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Chloramphenicol palmitate	50.00
60.00	2	Lutrol E 400	50.00
40.00	3	Cremophor RH 40	40.00
400.00	4	Sucrose	400.00
450.00	5	Water, purified	450.00
q.s.	6	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 to 3 in a suitable stainless steel-jacketed vessel. Heat to 70˚C to obtain a clear solution.
2. Cool to 40˚C.
3. In a separate vessel, add and dissolve items 4 and 5 and then add this solution to step 2.
4. Bring to volume with item 6. Mix.

Chloroxylenol Surgical Scrub

Chloroxylenol 3% and cocamidopropyl PG-dimonium chloride phosphate 3%. Inactive ingredients: water, sodium lauryl sulfate, cocamide DEA, propylene glycol, cocamidopropyl betaine, citric acid, tetrasodium EDTA, aloe vera gel, hydrolyzed animal protein, D&C yellow no. 10. In addition, chloroxylenol 5%, terpineol 10%, absolute alcohol 20%, soft potassium soap 8.5%, and caramel 25% and lemon oil q.s. in a water base.

Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.00	1	Chlorpheniramine maleate	0.40
3000.00	2	Sucrose	600.00
4.50	3	Methyl paraben	0.90
1.50	4	Propyl paraben	0.30
1.00	5	Citric acid (monohydrate)	0.20
2.40	6	Sodium citrate	0.48
2.00	7	Banana green flavor	0.40
—	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 500.0 g of item 8 to the manufacturing vessel and heat to 95° to 98°C.
2. Add items 3 and 4 while mixing to dissolve at high speed.
3. Mix for 5 minutes. Add item 2 while mixing at slow speed. Temperature 95° to 98°C.
4. Mix for 1 hour at high speed. Cool down to 30°C while mixing at slow speed.
5. Dissolve items 5 and 6 in 20.0 g of cooled item 8 (25°C).
6. Transfer the solution to the manufacturing vessel above while mixing at high speed. Mix for 2 minutes.
7. Add 8.0 g of cold item 8 (25° to 30°C) in a separate container and dissolve item 1 by using stirrer. Mix for 10 minutes and transfer to the manufacturing vessel above.
8. Rinse the container with 2.0 g of cooled item 8 (25°C) and transfer the rinsings to the manufacturing vessel while mixing at high speed.
9. Add item 7 to the manufacturing vessel while mixing.
10. Mix for 10 minutes at high speed. Make up the volume up to 1 L with item 8 and finally mix for 15 to 20 minutes at high speed.
11. Check and record the pH. Limit 5.0 to 5.2 at 25°C. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
12. Filter the syrup at 1.5 bar. Bubble the syrup with nitrogen gas.

Ciclopirox Topical Solution

Each gram of PENLAC NAIL LACQUER (ciclopirox) topical solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, isopropyl alcohol, and butyl monoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
80.00	1	Ciclopirox	80.00
330.00	2	Ethyl acetate	330.00
300.00	3	Butyl monoester of poly[methylvinyl ether/maleic acid] in isopropyl alcohol (50%)	300.00
q.s.	4	Isopropyl alcohol	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 4 in a suitable stainless steel vessel in an explosion-proof room.
2. Add item 2 and item 3 in a separate vessel, mix, and add to step 1.
3. Add item 1 and mix; seal immediately.

Cimetidine Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L(g)**
200.00	1	Cimetidine USE cimetidine hydrochloride	45.80
0.161 mL	2	Alcohol	32.50 mL
5.00	3	Methyl paraben	1.00
1.00	4	Propyl paraben	0.20
20.00	5	Pluronic F68	4.00
0.50 mL	6	Propylene glycol	100 mL
20.00	7	Saccharin sodium	4.00
15.00	8	Sodium chloride	3.00
27.00	9	Disodium hydrogen phosphate	5.40
0.50 mL	10	Sorbitol solution 70%	100 mL
2.07 g	11	Sucrose	414.00
0.05	11	Yellow dye	0.01
0.0014	12	Flavor	0.28 mL
0.0014	13	Flavor	0.28 mL
2.00	14	Sweetener additional	0.40
q.s.	15	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 3 and 4 in a stainless steel vessel and add 70% item 15; heat to 80 to 90°C to dissolve.
2. In a separate vessel, add and mix items 5 through 11.
3. Add step 2 to step 1.
4. Add and dissolve remaining items and mix.
5. Fill.

Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension

Ciprofloxacin hydrochloride and hydrocortisone otic suspension contains the synthetic broad spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, hydrocortisone, in a preserved, nonsterile suspension for otic use. Each milliliter contains ciprofloxacin hydrochloride (equivalent to 2 mg ciprofloxacin), 10 mg hydrocortisone, and 9 mg benzyl alcohol as a preservative. The inactive ingredients are polyvinyl alcohol, sodium chloride, sodium acetate, glacial acetic acid, phospholipon 90HB (modified lecithin), polysorbate, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.00	1	Ciprofloxacin (use ciprofloxacin hydrochloride)	2.33
10.00	2	Hydrocortisone	10.00
1.00	3	Polysorbate 80	1.00
20.00	4	Polyvinyl alcohol	20.00
1.50	5	Phospholipon 90H (lecithin)	1.50
9.00	6	Benzyl alcohol	9.00
7.00	7	Acetic acid glacial	7.00
4.10	8	Sodium acetate trihydrate	4.10
9.00	9	Sodium chloride	9.00
q.s.	10	Hydrochloric acid 1 N for pH adjustment	q.s.
q.s.	11	Sodium hydroxide 1 N for pH adjustment	q.s.
q.s.	12	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Use well-passivated stainless steel vessels; use only sodium vapor lamps or yellow light in the manufacturing area. Avoid forming foam during transfer of liquids.
2. Charge approximately 1 L of item 12 in a suitable vessel and heat to 90° to 95°C and then cool to 20° to 25°C under a nitrogen environment, and hold for later use for premixing, rinsing, and final volume makeup.
3. To 50% of volume of item 11 add item 4 at 90° to 95°C.
4. Add and mix item 5 while maintaining nitrogen blanket cover. Cool to 40° to 50°C.
5. Add and mix item 6 and cool to 20° to 25°C.
6. In a separate vessel, mix acetic acid, sodium chloride and sodium acetate trihydrate in about 10% of item 12 as prepared in step 1.
7. In a separate vessel charge item 2 and item 3 and 30% of item 12, mix, and then pass through a micronizing chamber.
8. Add to step 6 and mix well.
9. Add item 1 to in a separate vessel and 20% of item 12 and portions of item 7 and then add to the main batch.
10. Bring to volume.
11. Adjust pH to 4.75 using item 10 or 11 as needed. Fill.

Cisapride Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	Cisapride USE: Cisapride monohydrate	1.04
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1000.00	4	Sucrose	200.00
50.00	5	Microcrystalline cellulose (Avicel RC 591)	10.00
12.50	6	Methylcellulose 4000	2.50
5.00	7	Sodium chloride	1.00
2.50	8	Polysorbate 80 (Tween 80)	0.50
2.50	9	All fruit flavor	0.50
—	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

Cisapride dispersion should be uniformity mixed or levigated. Avicel RC-591 and Methyl Cellulose dispersion should be uniform and smooth.

1. Mix item 8 in 100.0 g of item 10 (35˚ to 40˚C) in a stainless steel vessel, using stirrer. Add item 1 and mix to make smooth dispersion and keep aside. Check the smoothness of dispersion.
2. Add 185.0 g of item 10 to a suitable mixer and heat to 90˚ to 95˚C. Dissolve items 2 and 3 while mixing. Add and dissolve item 4 while mixing.
3. Cool down to about 50˚ to 55˚C.
4. Filter the syrup through T1500 filter pads (8 to 10) washed with purified water. Collect the syrup in clean stainless steel tank. Avoid any loss of syrup quantity.
5. Disperse item 6 in 150.0 g of hot item 10 (70˚ to 80˚C) in mixer while mixing.
6. Mix and homogenize at temperature 70˚ to 80˚C, mixer speed 18 rpm, homogenizer high speed and vacuum 0.4 to 0.6 bar for 5 minutes.
7. Cool down to 25˚ to 30˚C with continuous mixing. Check the smoothness of dispersion.
8. Disperse item 5 in 250.0 g of item 10 (25˚ to 30˚C) in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes to make smooth dispersion. Check the smoothness of dispersion.
9. Transfer syrup mixer. Transfer Avicel mucilage to mixer.
10. Mix at high homogenizer speed and under vacuum for 5 minutes.
11. Dissolve item 7 in 10.0 g of item 10 and add to mixer while mixing. Add drug dispersion to mixer.
12. Rinse the drug container with 40.0 g of item 10 and add the rinsing to mixer.
13. Add item 9 to mixer while mixing.
14. Add item 10 up to final volume 1 L.
15. Finally mix and homogenize for 5 minutes at mixer speed 18 rpm, homogenizer at high speed, vacuum 0.4 to 0.6 bar.
16. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to the stainless steel storage tank, previously sanitized.

Citalopram Hydrobromide Oral Solution

Celexa oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

Clarithromycin Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/Kg (g)**
125.00	1	Clarithromycin	35.47
	2	Carbopol 974P	21.28
	3	Polyvinyl pyrrolidone K90	4.96
	4	Water, purified	145 mL
	5	Hydroxypropyl methylcellulose phthalate HP-55	43.17
	6	Castor oil	4.56
q.s.	7	Acetone, approximate	172 mL
q.s.	8	Ethanol, approximate	164 mL
	9	Potassium sorbate	5.96
	10	Sucrose	600.80
	11	Maltodextrin	67.58
	12	Water, purified	10 mL
	13	Xanthan gum	1.08
	14	Flavor dry	10.14
	15	Silicon dioxide	1.42
	16	Citric acid	1.20
	17	Titanium dioxide	10.14
	18	Maltodextrin	13.50
q.s.	19	Sucrose	q.s. to 1 Kg

MANUFACTURING DIRECTIONS

1. This product requires coated clarithtomycin granules. Add polyvinyl pyrrolidone to water and mix.
2. Use water to granulate a blend of clarithromycin and Carbopol 974P.
3. Dry granules at 70˚C until loss on drying is not more than (NMT) 5%.
4. Collect fraction between 177 and 420 microns.
5. Regranulate smaller particles to meet the above range.
6. Blend the regranulate in step 5 to step 6.
7. Prepare coating solution by adding ethanol and acetone and hydroxyupropyl methylcellulose phthate and castor oil in a mixing vessel; mix until solution is clear.
8. Coat granules in step 6 in a particle coater and dry to loss on drying of NMT 5%.
9. Sift coated granules and retain the fraction between 149 and 590 microns.
10. In a separate vessel, dissolve potassium sorbate in purified water.
11. Blend sucrose and the maltodextrin until a homogenous mix is achieved.
12. Granulate the step 11 mixture with step 10.
13. Dry the granulation until loss on drying is NMT 1%.
14. Mill dried granules and blend.
15. Mix to clarithromycin-coated granules in appropriate quantity, add silicon dixode, and blend. Fill appropriate quantity.

Clindamycin Phosphate Topical Solution

CLEOCIN T topical solution and CLEOCIN T topical lotion contain clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per milliliter. CLEOCIN T topical gel contains clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per gram. Each CLEOCIN T topical solution pledget applicator contains approximately 1 mL of topical solution. Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water.

Clotrimazol Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
30.00	1	Clotrimazole	30.00
300.00	2	Cremophor RH 40	300.00
q.s.	3	Preservatives	q.s.
340.00	4	Alcohol	340.00
330.00	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 1 and 2 in a stainless steel-jacketed mixing vessel. Heat to 60˚C and mix well.
2. In a separate vessel, charge items 3 to 5 at 90˚C and add to step 1.
3. Mix well and fill.

Codeine Phosphate and Acetaminophen Elixir

Each 5 mL of elixir contains codeine phosphate 12 mg, acetaminophen 120 mg, alcohol 7%, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, and FD&C yellow no. 6.

Colistin Sulfate, Neomycin, Thonzonium Bromide, and Hydrocortisone Otic Suspension

Cortisporin-TC otic suspension with neomycin and hydrocortisone (colistin sulfate–neomycin sulfate–thonzonium bromide–hydrocortisone acetate otic suspension) is a sterile aqueous suspension containing in each milliliter: colistin base activity, 3 mg (as the sulfate); neomycin base activity, 3.3 mg (as the sulfate); hydrocortisone acetate, 10 mg (1%); thonzonium bromide, 0.5 mg (0.05%); polysorbate 80, acetic acid, and sodium acetate in a buffered aqueous vehicle. Thimerosal (mercury derivative), 0.002%, is added as a preservative. The suspension is a nonviscous liquid, buffered at pH 5, for instillation into the canal of the external ear or direct application to the affected aural skin.

Cotrimoxazole Oral Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40.00	1	Trimethoprim micronized (98% particles below 50 microns)	8.00
200.00	2	Sulfamethoxazole powder (100% particles below 50 microns)	40.00
20.00	3	Magnesium aluminum silicate (Veegum HV)	4.00
22.50	4	Carboxymethylcellulose sodium	4.50
350.00	5	Glycerin	70.00
400.00	6	Propylene glycol	80.00
5.00	7	Polyvinyl pyrrolidone (polyvinyl pyrrolidone K-30)	1.00
20.00	8	Polysorbate 80	4.00
12.50	9	Colloidal silicon dioxide (aerosil 200)	2.50
375.00	10	Sorbitol (70% solution)	75.00
5.00	11	Saccharin sodium	1.00
3.00	12	Citric acid	0.60
2200.00	13	Sucrose	440.00
5.00	14	Methyl paraben	1.00
1.50	15	Propyl paraben	0.30
0.035	16	Raspberry red color	0.007
0.025	17	FD&C red no. 40	0.005
5.00	18	Banana flavor	1.00
5.00	19	Apricot flavor	1.00
—	20	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Disperse item 4 in item 5 in a stainless steel vessel using stirrer. Check that the dispersion is even.
2. Disperse item 3 in the dispersion of items 4 and 5 (Sodium CMC-Glycerol) at step 1, using stirrer. Check that the final dispersion is even.
3. Add 100.0 g of hot item 20 (75° to 85°C) to the dispersion at step 2 while stirring to make the mucilage. Mix for 30 minutes using stirrer.
4. Keep aside the mucilage, for hydration, overnight in a well-closed container.
5. Add item 6 in a stainless steel container and mix items 2 and 1 while mixing using stirrer to make homogenous slurry.
6. Add 100.0 g of cold item 20 (25° to 30°C) in a stainless steel container and dissolve item 7 to make a clear solution. Add item 8 while mixing to make a clear solution, then add item 9 while mixing at slow speed.
7. Transfer the mix from step 4.1 to the slurry of Sulpha-Trimethoprim step 3 while mixing.
8. Mix for 30 minutes.
9. Add item 10 to the slurry. Mix for 10 minutes.
10. Add 250.0 g of item 20 in mixer and heat to 90° to 95°C. Add items 14 and 15 while mixing to dissolve, homogenize at high speed for 2 minutes.
11. Add item 13 to the Parabens solution at step 6. Mix well to dissolve completely.
12. Cool down to 30°C.
13. Filter the syrup through T-1500 filters using filter press. (Wash the filters with cooled item 20 about 100 mL before use.) Collect the filtered syrup in stainless steel containers.
14. Wash the mixer with item 20.
15. Load items 4 and 3 (CMC-Veegum) mucilage from step 2 to the mixer. Homogenize while mixing for 2 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C. Check the suspension for uniformity.
16. Load the sulpha-trimethoprim slurry from step 5 to the mixer. Homogenize while mixing for 10 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C, Check the suspension for uniformity.
17. Transfer the sugar syrup from step 7 to the mixer. Homogenize while mixing for 2 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C. Check the suspension for uniformity.
18. Dissolve item 12 in 4.0 g of cooled item 20 and transfer to the mixer while mixing.
19. Dissolve item 11 in 10.0 g of cooled item 20 and transfer to the mixer while mixing.

20. Dissolve items 16 and 17 and FD&C red 40 in 1.0 g of cooled item 20 and transfer to the mixer while mixing.
21. Mix items 18 and 19 and transfer to the mixer while mixing.
22. Add cold item 20 to makeup the volume to 1 L.
23. Set the mixer on high speed, rpm 20, manual mode, vacuum 0.4 to 0.6 bar, temperature 25˚C, Mix for 15 minutes.
24. Check and record the pH. Limit 5.5 to 5.8 at 25˚C. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
25. Transfer the suspension through 630-micron sieve to the stainless steel storage tank, previously sanitized by 70% ethanol.

Cromolyn Sodium Nasal Spray

Each milliliter of NASALCROM nasal spray contains 40 mg of cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution. Each metered spray releases the same amount of medicine: 5.2 mg cromolyn sodium.

Cromolyn Sodium Oral Concentrate

Each 5-mL ampule of oral concentrate contains 100 mg cromolyn sodium, in purified water. It is an unpreserved, colorless solution supplied in a low-density polyethylene plastic unit-dose ampule with 8 ampules per foil pouch.

Cyclosporin Oral Solution

Cyclosporine oral solution: each milliliter contains cyclosporin 100 mg and alcohol 12.5% by volume dissolved in an olive oil, Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle that must be further diluted with milk, chocolate milk, or orange juice before oral administration.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.00	1	Cyclosporin	100.00
125.00	2	Alcohol	125.00
532.00	3	Olive oil	532.00
242.50	4	Labrafil M 1944CS	242.50

MANUFACTURING DIRECTIONS

1. Charge items 2 to 4 in a mixing vessel and stir well.
2. Homogenize step 1.
3. Add item 1 and homogenize again.
4. Fill.

Cyclosporine Soft Gelatin Capsules

Cyclosporine capsules are available in 25 mg and 100 mg strengths. Each 25- or 100-mg capsule contains cyclosporine 25 mg and alcohol 12.7% by volume. Inactive ingredients: corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolysed glycerides), red iron oxide (25 mg and 100 mg capsule only), sorbitol, titanium dioxide, and other ingredients.

Desmopressin Acetate Nasal Spray

Desmopressin acetate is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin, an antidiuretic hormone affecting renal water conservation. It contains 1.5 mg/mL desmopressin acetate in a pH-adjusted aqueous solution with hydrochloric acid to 4.0: Chlorobutanol (5.0 mg) and sodium chloride (9.0 mg) are the inactive ingredients. The compression pump delivers 0.1 mL (150 μg) of solution per spray; 2.5 mL bottle.

Dexamethasone Elixir

Dexamethasone elixir contains 0.5 mg of dexamethasone in each 5 mL. Benzoic acid, 0.1%, is added as a preservative. It also contains alcohol 5%. Inactive ingredients are FD&C red no. 40, flavors, glycerin, purified water, and sodium saccharin.

Dextromethorphan Solution

Bill of Materials			
Scale mg/mg	**Item**	**Material Name**	**Quantity/kg (g)**
14.70	1	Dextromethorphan base	14.70
q.s.	2	Vehicle (Pluronic F 127 55.51%, ethanol 26.48% and water 18.01%)	q.s. to 1 kg
3.00	3	Sodium saccharin	3.00
q.s.	4	Flavors and colors	q.s.
0.50	5	Monoammonium glycerhizzinate	0.50

MANUFACTURING DIRECTIONS

1. Add the dextromethorphan base, sodium saccharin, and monoammonium glycerizzinate into a clean vessel.
2. Add ethanol and then the poloxamer and water. Mix until clear and uniform.
3. Good pourable formula.

Dextromethorphan and Chlorpheniramine Maleate Solution

Bill of Materials			
Scale (mg/mg)	**Item**	**Material Name**	**Quantity/Kg (g)**
14.70	1	Dextromethorphan base	14.70
2.60	2	Chlorpheniramine maleate	
q.s.	2	Vehicle (Pluronic F 127 55.67%, ethanol 26.55% and water 17.79%)	q.s. to 1 Kg
3.00	3	Sodium saccharin	3.00
q.s.	4	Flavors and colors (menthol, eucalyptus oil, tienzoocane)	q.s.
0.50	5	Monoammonium glycerhizzinate	0.50

MANUFACTURING DIRECTIONS

1. Mill and screen the menthol and tienzoocaine to reduce the product particle size.
2. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycerizzinate into a clean vessel.
3. Add eucalyptus oil and ethanol to the vessel.
4. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Dextromethorphan Liquid

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
22.00	1	Dextromethorphan base	22.00
q.s.	2	Vehicle (Pluronic 33.56%, ethanol 10.51%, water 13.42%, propylene glycol 42.51%) [a]	q.s. to 1 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00
4.00	5	Sodium saccharin	4.00
1.50	6	Monoammonium glycerhizzinate	1.50
5.00	7	Acesulfame	5.00
14.00	8	Flavor	14.00

[a]Alternate vehicle composition: pluronic F 27 29.08%, ethanol 10.51%, water 24.61%, propylene glycol 35.80%. Second alternate vehicle: pluronic F127 40.27%, ethanol 10.51%, water 13.42%, propylene glycol 35.80%.

MANUFACTURING DIRECTIONS

1. Add propylene glycol and poloxamer to a clean vessel (main mix).
2. While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer.
3. Once a uniform solution is obtained, remove from heat source and continue mixing.
4. In a separate vessel (alcohol premix) add alcohol, dextromethorphan base, and monoammonium glycerizzinate and mix until uniform.
5. In another vessel (water premix), add water, EDTA, sodium saccharin, acesulfame, and sodium metabisulfite. Mix until all materials are dissolved.
6. Add the alcohol containing premix to the main mixing vessel containing the poloxamer.
7. Mix until uniform.
8. While stirring, add the water containing premix to the main vessel and continue to mix until uniform.
9. Add desired flavor component and mix until uniform.
10. The preparation has a viscosity of approximately 0.67 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 10.5. If using alternate vehicle composition (above), the preparation has a viscosity of approximately 0.97 Pascal seconds and a triggered viscosity ratio at a 50% dilution with water of 4.95. If using the second alternate vehicle, the preparation has a viscosity of approximately 2.14 Pascal seconds and a triggered viscosity ratio at a 50% dilution.

Dextromethorphan Liquid

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (pluraflo 1220 40.90%, ethanol 10.22%, propylene glycol 46.83%, anhydrous glycerin 2.05%)	q.s. to 1 L
22.00	2	Dextromethorphan base	22.00
q.s.	3	Flavors	q.s.

MANUFACTURING DIRECTIONS

1. Weigh the dextomethophan into a clean vessel, add the ethanol, and begin mixing.
2. Add propylene glycol and mix until uniform and clear.
3. Add pluraflo and mix. Add glycerin and mix until uniform.
4. Add desired flavor component and mix until uniform.

Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Dextromethorphan hydrobromide	20.00
40.00	2	D-Pseudoephedrine hydrochloride	40.00
4.00	3	Chlorpheniramine maleate	4.00
250.00	4	Sorbitol syrup	250.00
2.00	5	Saccharin sodium	2.00
30.00	6	Hydroxyethyl cellulose (Natrosol HHY)	30.00
25.00	7	Sodium benzoate	25.00
10.50	8	Banana flavor	10.50
11.00	9	Custard flavor	11.00
12.00	10	Trisodium citrate dihydrate powder	12.00
q.s.	11	Water, purified	q.s.

MANUFACTURING DIRECTIONS

1. In a suitable vessel, add sorbitol syrup and hydroxyethylcellulose and purified water; mix well.
2. Add sodium benzoate and stir again for 5 minutes.
3. After obtaining clear solution, put under stirring hydroxyethyl cellulose suspension, rinse the container with purified water, and transfer the rinsing to the vessel.
4. Heat the vessel to 40˚ to 50˚C and keep the mix stirring for 1 hour.
5. After 1 hour, a clear gel without lumps is obtained.
6. The gel is then diluted with sorbitol syrup and cooled to 30˚C.
7. In a separate vessel, add purified water and heat under stirring to 50˚C.
8. After reaching this temperature, dissolve sequentially, dextromethorphan hydrobromide, chlorpheniramine maleate and pseudoephedrine hydrochloride,and saccharin sodium.
9. Cool the solution to 25˚C.
10. In a suitable stainless steel container, add purified water and under stirring dissolve trisodium citrate under 00.6 bar and high speed.
11. The active substance solution from step 10 is transferred to the syrup vehicle.
12. The vessel is rinsed twice with purified water.
13. In the larger vessel, add under stirring (low) the custard flavor and banana flavor, and mix for 10 minutes.
14. Then, under stirring, add the solution from step 13; keep stirring for 15 minutes at moderate speed.
15. Stop stirring and check pH (5.9 to 6.2); adjust with 10% trisodium citrate solution; after each addition, where necessary, stir for 5 minutes before recording pH again.
16. Finally, make up the volume with purified water and stir once more for 15 minutes under vacuum (–0.6 bar) moderate speed. Stop stirring and vacuum; check final volume once more.
17. Clear syrup is filtered under compressed air pressure first through a filter of 330 microns and then through a 20-micron filter of propylene type.

Dextrose, Levulose, and Phosphoric Acid Solution

EMETROL is an oral solution containing balanced amounts of dextrose (glucose) and levulose (fructose) and phosphoric acid with controlled hydrogen ion concentration. Available in original lemon-mint or cherry flavor. Each 5-mL teaspoonful contains dextrose (glucose), 1.87 g; levulose (fructose), 1.87 g; phosphoric acid, 21.5 mg; glycerin; methylparaben; purified water; and D&C yellow no. 10 and natural lemon-mint flavor in lemon–mint Emetrol and FD&C red no. 40 and artificial cherry flavor in cherry Emetrol.

Diclofenac Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
15.00	1	Diclofenac sodium	15.00
25.00	2	Kollidon 30	24.00
5.00	3	Cremophor RH 40	5.00
400.00	4	Sucrose crystalline	400.00
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve items 2 to 5 in a suitable stainless steel vessel.
2. Add item 1 and dissolve.
3. Fill.

Diazepam Rectal Solution

Bill of Materials			
Scale (mg/2.5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Diazepam	4.00
2.50	2	Benzoic acid	1.00
250.00	3	Alcohol	100.00
1000.00	4	Propylene glycol	400.00
122.50	5	Sodium benzoate	49.00
37.50	6	Benzyl alcohol	19.00
q.s.	7	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve benzoic acid in absolute alcohol previously warmed to 35˚C.
2. Add diazepam to step 1, stir to dissolve.
3. Separately mix together polypropylene glycol and benzyl alcohol.
4. Separately dissolve sodium benzoate in one-fourth quantity of purified water and filter through a 0.6-μm Millipore filter.
5. Under heavy stirring, mix together steps 2 and 3.
6. Bring to volume with water under stirring and filter through a 0.22-μ Millipore filter.
7. Fill solution into rectal tubes; fill volume 2.9 mL.

Didanosine for Oral Solution

VIDEX buffered powder for oral solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets of each product strength also contain a citrate–phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose.

Digoxin Capsules

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides"). The capsule is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin dissolved in a solvent comprising polyethylene glycol 400, 8% ethyl alcohol, propylene glycol, and purified water. Inactive ingredients in the capsule shell include FD&C red no. 40 (0.05-mg capsule), D&C yellow no. 10 (0.1-mg and 0.2-mg capsules), FD&C blue no. 1 (0.2-mg capsule), gelatin, glycerin, methylparaben and propylparaben (added as preservatives), purified water, and sorbitol. Capsules are printed with edible ink.

Digoxin Elixir Pediatric

This is a stable solution of digoxin specially formulated for oral use in infants and children. Each milliliter contains 50 mcg (0.05 mg) digoxin. The lime-flavored elixir contains the inactive ingredients alcohol 10%, methylparaben 0.1% (added as a preservative), citric acid, D&C green no. 5, D&C yellow no. 10, flavor, propylene glycol, sodium phosphate, and sucrose. Each package is supplied with a specially calibrated dropper to facilitate the administration of accurate dosage even in premature infants. Starting at 0.2 mL, this 1-mL dropper is marked in divisions of 0.1 mL, each corresponding to 5 mcg (0.005 mg) digoxin.

Dihydroergotamine Mesylate Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.00	1	Dihydroergotamine mesylate, 10% excess	2.20
153.00	2	Glycerin	153.00
48.25	3	Alcohol	48.25
q.s.	4	Methanesulfonic acid	q.s.
q.s.	5	Sodium hydroxide	q.s.
q.s.	6	Water purified	q.s. to 1 L
q.s.	7	Nitrogen gas	q.s.

MANUFACTURING DIRECTIONS

The product is highly susceptible to oxidation and should be manufactured until continuous bubbling and cover of nitrogen; the oxygen level should be below 1.00 ppm at all times; nitrogen gas used should filtered through a 0.45-micron membrane filter; also, protect product from light; all tubing used for transferring product should be of stainless steel, Teflon, or silicon.

1. Heat sufficient quantity of item 6 to 95˚C and hold for 1 hour. Begin bubbling nitrogen for 1 hour; cool slowly to 22˚C while continuing to bubble nitrogen.
2. In another suitable glass-lined or stainless-steel container, charge glycerin.
3. In another stainless-steel container, charge alcohol and bubble it with nitrogen for more than 2 hours.
4. Check oxygen levels in step 1 to less than 1.00 ppm.
5. Flush a suitable tank with nitrogen and transfer approximately 700 mL of purified water from step above and begin bubbling nitrogen.
6. Add approximately 40 mL of purified water from step 4 to step 2 and bubble nitrogen again for 1 hour; do not discontinue bubbling throughout manufacturing process.
7. Weigh the alcohol container above, add 49 g of alcohol to water in step above, stir.
8. Dilute about 0.03 mL of methanesulfonic acid with purified water to make a 20% solution; measure and adjust pH to 3.25.
9. Add item 1 to batch and stir until completely dissolved.
10. Add glycerin/water mixture to the batch and adjust volume to 995 mL.
11. Dissolve 4 g of sodium hydroxide in 100 mL purified water and use this solution to adjust pH of step 10 to 3.75; stir for 1 minute and recirculate for at least 5 minutes.
12. Adjust the volume to 1 L with item 6.
13. Filter through 0.22-micron filter previously sterilized and fill in presterilized amber-colored bottle with nitrogen flushing.

Diphenhydramine and Ammonium Chloride Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
131.50	1	Ammonium chloride	26.30
15.00	2	Caramel	5.00
11.00	3	Citric acid	2.20
13.50	4	Diphenhydramine hydrochloride	2.70
200.00	5	Alcohol	40.00
318.00	6	Glycerin	63.60
1.10	7	Menthol	0.22
5.00	8	Flavor	1.00
9.80	9	Saccharin sodium	1.96
12.00	10	Sodium benzoate	2.40
2750.00	11	Sugar	550.00
q.s.	12	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge one-half of item 12 in a suitable stainless steel mixing vessel, heat to 90° to 95°C, and add and mix item 11. Mix for 1 hour at 90° to 95°C.
2. Cool to room temperature.
3. In separate vessels, charge 100 mL of item 12 in each and mix items 3, 4, or 10 separately. Then mix them all together and stir well.
4. Add item 6 to step 2 and mix well.
5. In 100 mL of water dissolve item 4 and add to step 4.
6. Dissolve item 2 in 100 mL of water and add to step 5.
7. In a separate vessel charge item 5 and add and mix items 7 and 8.
8. Add step 7 into step 6 and make up volume.

Diphenhydramine Hydrochloride Liquid

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
12.50	1	Diphenhydramine hydrochloride	2.50
1000.00	2	Lycasin 80/55	200.00
12.00	3	Sodium benzoate	2.40
4.40	4	Citric acid monohydrate	0.88
7.60	5	Sodium citrate	1.52
5.00	6	Saccharin sodium	1.00
250.00	7	Propylene glycol	50.00
1.25	8	Menthol	2.50
5.00	9	Flavor	1.00
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 600 mL of item 10 in a stainless steel vessel and bring to boil, cool to 40˚ to 50˚C.
2. Add and mix items 2 to 4 and stir to dissolve; mix for another 10 minutes.
3. In a separate vessel charge 100 mL of item 10 and add and mix item 6.
4. In a separate vessel charge 100 mL of item 10 and add and mix item 1. Add to step 1.
5. Add steps 2 and 3 to step 1 and mix well.
6. Add item 2 and mix again.
7. In a separate vessel add and mix item 7 to 9. Add to step 6 and make up volume.
8. Fill.

Dornase Alfa Inhalation Solution

Each PULMOZYME single-use ampule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.

Doxercalciferol Capsules

Doxercalciferol, the active ingredient in Hectorol, is a synthetic vitamin D analog that undergoes metabolic activation *in vivo* to form 1(alpha),25-dihydroxyvitamin D2 (1(alpha),25-$(OH)_2$D2), a naturally occurring, biologically active form of vitamin D2. Hectorol is available as soft gelatin capsules containing 2.5 mcg doxercalciferol. Each capsule also contains fractionated triglyceride of coconut oil, ethanol, and butylated hydroxyanisole. The capsule shells contain gelatin, glycerin, titanium dioxide, and D&C yellow no. 10.

Dyphylline, Guaifenesin Elixir

Each 15 mL (one tablespoonful) of elixir contains dyphylline 100 mg, guaifenesin 100 mg, alcohol (by volume) 17%, citric acid, FD&C yellow no. 6, flavor (artificial), purified water, saccharin sodium, sodium citrate, and sucrose.

Electrolyte Lavage Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
60.00	1	Polyethylene glycol 3350	60.00
1.46	2	Sodium chloride	1.46
0.75	3	Potassium chloride	0.75
1.68	4	Sodium bicarbonate	1.68
5.68	5	Sodium sulfate	5.68
0.81	6	Flavor	0.81

MANUFACTURING DIRECTIONS

The values given above pertain to solution on reconstitution of one flavor pack. When dissolved in sufficient water to make 4 L, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride, and 18 mEq/L polyethylene glycol 3350. The reconstituted solution is isosmotic and has a mild, salty taste. Colyte Flavor Packs are available in citrus berry, lemon lime, cherry, and pineapple. This preparation can be used without the Colyte Flavor Packs and is administered orally or via a nasogastric tube. Each Citrus Berry Flavor Pack (3.22 g) contains hydroxypropyl methylcellulose 2910, citrus berry powder, saccharin sodium, and colloidal silicon dioxide. Each Lemon Lime Flavor Pack (3.22 g) contains lemon-lime NTA powder, hydroxypropyl methylcellulose 2910, Prosweet® Powder Natural, saccharin sodium, and colloidal silicon dioxide. Each Cherry Flavor Pack (3.22 g) contains hydroxypropyl methylcellulose 2910, artificial cherry powder, saccharin sodium, and colloidal silicon dioxide. Each Pineapple Flavor Pack (3.22 g) contains hydroxypropyl methylcellulose 2910, pineapple flavor powder, Magna Sweet, saccharin sodium, and colloidal silicon dioxide.

Erythromycin Drops

Bill of Materials			
Scale (mg/2.5 mL)	**Item**	**Material Name**	**Quantity/kg (g)**
	1	Sodium carboxymethyl cellulose	0.41
	2	Dye red FD&C no. 3	0.13
	3	Sucrose	796.81
	4	Sodium citrate dihydrate	52.60
	5	Sodium carboxy methyl cellulose	13.10
	6	Magnesium aluminum silicate type IB veegum F	7.90
	7	Water, purified	66 mL
100.00	8	Erythromycin USE erythromycin ethylsuccinate citrate, washed (850 mcg/mg)	123.50
	9	Flavor	3.94

MANUFACTURING DIRECTIONS

Erythromycin ethylsuccinate (item 9) is factored in based on the potency used in the Bill of Materials. Excess of up to 5% erythromycin may be included. The weight of sugar (item 3) is adjusted to compensate for potency variation and excess of the erythromycin ethylsuccinate, to maintain the standard quantity at 1000 g.

1. Dissolve the sodium carboxymethylcellulose (item 1) and the dye (if used) in 50 mL hot purified water. Stir until the sodium carboxymethylcellulose is completely in solution. Allow to cool before using.
2. Screen the sucrose through a 2-mm-aperture screen into a mixer.
3. Mill the remaining ingredients, with the exception of the flavor, through a 1-B band (1.27 mm aperture, or similar) or 0 band (686 micron aperture, or similar) with impact forward at high speed, or screen through a 840-micron aperture screen.
4. Load the milled or screened ingredients into the mixer with the screened sucrose, and dry blend for not less than 5 minutes.
5. Mass with the solution from step 1 and q.s. using purified water, if necessary. Mixer must not be stopped and the sides must be scraped down several times during the massing operation, to minimize the presence of white particles in the final granulation. Do not allow massed granules to stand.
6. Screen the wet mass through a 16-mm-aperture mesh (hammer mill) or a 4-mm-aperture screen (oscillating granulator) and spread evenly onto trays.
7. Dry granules in an oven at between 49° and 55°C, to not more than 1.0% loss on drying (15 minutes Brabender, or equivalent, at 105°C), or loss on drying at 60°C at 5 mm of mercury for 3 hours.
8. Screen the cooled, dried granules through a 1.19-mm-aperture screen and grind coarse through 2-AA band (1.98 mm aperture, or similar), medium speed, knives forward, or screen through a 1.4-mm-aperture screen on an oscillating granulator. Protect granules from excessive exposure to moisture.
9. Screen the flavor through a 600-micron-aperture screen with an equal portion of granulation.
10. Fill into suitable approved bottles at the theoretical fill weight.

Erythromycin Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
500.00	1	Polyethylene glycol 400	100.00
20.00	2	Erythromycin, USE erythromycin base, 15% excess	25.55
0.32	3	Acetone	65.40 mL
77% (v/v)	4	Alcohol	840.00 mL
q.s.	5	Nitrogen gas	q.s.

MANUFACTURING DIRECTIONS

Product is sensitive to moisture. Every effort should be made to avoid exposure or incorporation of moisture into the product because the stability of the final product is affected. Check mixing tank to make sure it is clean and dry. Mixing tank must be purged with nitrogen gas, as directed, at the start of and during manufacture to replace most of the air in the mixing tank and to reduce the possibility of fire or explosion if there should be a spark. Transfer and filling hose lines must be approved for use with solvents.

1. Charge polyethtylene glycol 400 to a suitable nitrogen-purged tank; keep nitrogen cover and purging on.
2. Add and mix acetone.
3. Add item 2 (quantity adjusted for potency) and mix.
4. Turn the agitator, sample, and adjust volume.

Estradiol Nasal Spray

Charge 2.6 g of estradiol into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved. After sealing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of at most 6.5 bar (20°C) in another pressure-addition vessel is added with stirring. The formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Ethchlorvynol Gelatin Capsule 200 mg

Bill of Materials			
Scale (mg/capsule)	**Item**	**Material Name**	**Quantity/1000 capsules (g)**
200.00	1	Ethchlorvynol	200.00
150.00	2	Polyethylene glycol 400	150.00
211.00	3	Gelatin colored opaque	211.00
—	4	Acetone, approximate[a]	86.00

[a]Used for cleaning purposes only and not present in final product.

MANUFACTURING DIRECTIONS

Polyethylene glycol should be weighed into clean, dry, light-resistant containers and sealed under nitrogen protection. Bulk container should be flushed with nitrogen and resealed.

1. Mix ethclorvynol, polyethylene glycol 400, and glycerin (if used) in an open stainless steel drum until uniform.
2. Cover with loose-fitting polyethylene cover, permitting gas to escape. Fumes will discolor metal. Retest if held for more than 1 month before encapsulating.
3. Mix gelatin to uniform consistency with minimal introduction of air. Encapsulate using the drug mixture into 1000 capsules using gelatin mass red opaque and 6.6 m size die roll.
4. Dry 3 days in a drying room at 20° to 22°C and 22 to 33% relative humidity or lower.
5. Inspect and remove culls. Optionally, wash with acetone or rinse twice with methylene chloride if used in place of acetone.
6. Finishing: Fill.

Eucalyptol Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
80.00	1	Eucalyptol	80.0
40.00	2	Cremophor RH 40	40.0
q.s.	3	Preservative	q.s.
q.s.	4	Water	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Mix eucalyptol and Cremophor at 65°C, stir well.
2. Add slowly the warm solution of item 3.
3. Clear or slightly opalescent, colorless liquid is desired.

Eucalyptus and Mint Emulsion

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
427.50	1	Distilled water	427.50
375.00	2	Eucalyptamint	375.00
70.00	3	Sodium stearoyl lactylate (pationic SSL)	70.00
35.00	4	PEG-20 hydrogenated lanolin (supersat ANS4)	35.00
17.50	5	Ritasynt IP	17.50
80.00	6	Cetearyl alcohol and polysorbate 60 and PEG-15 stearate and steareth-20 (Ritachol 1000)	80.00

MANUFACTURING DIRECTIONS

1. Heat item 1 to 71˚C.
2. Combine rest of the ingredients in another container and heat to 71˚C as well.
3. Slowly add water at 71˚C and mix for 1 hour. Cool the mixture to 35˚ to 45˚C and fill.

Fentanyl Citrate Nasal Spray

Charge 2.6 g of fentanyl citrate into a pressure addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved. After sealing and evacuation thereof, 6.7 kg of HFA 134a, which has previously been aerated with carbon dioxide and adjusted to a pressure of at most 6.5 bar (20˚C) in another pressure addition vessel, is added with stirring. The formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
75.00[a]	1	Ferrous sulfate	125.00
294.00	2	Sucrose	490.00
147.00	3	Maltitol solution (lycasin 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.060	6	FD&C yellow no. 6 (sunset yellow FCF)	1.00
3.120	7	Guarana flavor 12144-33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
—	10	Water, purified	q.s. to 1 L

[a]Equivalent to 15 mg iron (Fe).

MANUFACTURING DIRECTIONS

Bubble nitrogen throughout the process. Check and record pH of item 10 (limit 5.0 to 6.5).

1. Collect 166.67 g of item 10 in mixer.
2. Heat to 90° to 95°C for 10 minutes.
3. Add item 8. Stir to dissolve to a clear solution.
4. Add item 2. Stir to dissolve to a clear solution.
5. Add item 3. Stir for 10 minutes and cool to 30° to 35°C.
6. Dissolve item 4 in 10.0 g of item 10 (30° to 35°C) and add to first step.
7. Dissolve item 9 in 10.0 g of item 10 (30° to 35°C) and add to first step.
8. Dissolve item 5 in 273.33 g of item 10 (30° to 35°C). Then add item 1 to the clear solution and dissolve slowly without aeration.
9. Add to mixer at first step.
10. Dissolve item 6 in 10.0 g of item 10 (25° to 30°C) and add to first step.
11. Add item 7 to first step. Mix at low speed for 10 minutes.
12. Make volume up to 1.0 L with item 10.
13. Check and record pH. Target pH: 2.20 (limit between 1.95 and 5.15).
14. Filter the drops with recirculation.
15. Transfer the filtered drops in storage vessel under nitrogen blanket.
16. Use nitrogen blanket in the tank throughout the storage and filling period.

Ferrous Sulfate Oral Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.000[a]	1	Ferrous sulfate	40.000
3350.000	2	Sucrose	670.000
750.000	3	Maltitol solution (lycasin 80/55)	150.000
4.166	4	Citric acid (monohydrate)	833.200
8.334	5	Citric acid (monohydrate)	1.667
0.500	6	Color	0.100
15.500	7	Flavor	3.100
—	8	Water, purified	q.s. to 1 L

[a]Equivalent to 40 mg elemental iron.

MANUFACTURING DIRECTIONS

Bubble nitrogen throughout the process.

1. Heat 300.0 g of item 8 to 95˚C.
2. Add item 2 while stirring at low speed.
3. Dissolve to clear solution by stirring at 95˚C.
4. Add item 3. Stir at low speed and cool to 25˚ to 30˚C.
5. Dissolve item 4 in 17.0 g of item 8 and add to first step.
6. Dissolve item 5 in 180.0 g of item 8 in a separate stainless steel container. Then add item 1 to the clear solution and dissolve slowly without aeration.
7. Add to first step.
8. Dissolve item 6 in 16.0 g of item 8 and add to first step.
9. Add item 7 to first step. Mix at low speed for 10 minutes.
10. Make volume up to 1 L with item 8. Check and record pH. Limit between 2.0 and 5.0. Filter the syrup at 1.5 bar.
11. Recirculate about 100 to 150 mL of syrup.
12. Use nitrogen blanket in the tank throughout the storage period.

Fluconazole Oral Suspension

Diflucan for oral suspension contains 350 or 1400 mg of fluconazole and the following inactive ingredients: sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum, and natural orange flavor. After reconstitution with 24 mL of distilled water or purified water, each milliliter of reconstituted suspension contains 10 or 40 mg of fluconazole.

Flunisolide Spray

Nasarel is a metered-dose manual-pump spray unit containing 0.025% w/w flunisolide in an aqueous medium containing benzalkonium chloride, butylated hydroxytoluene, citric acid, edetate disodium, polyethylene glycol 400, polysorbate 20, propylene glycol, sodium citrate dihydrate, sorbitol, and purified water. Sodium hydroxide or hydrochloric acid may be added to adjust the pH to approximately 5.2. It contains no fluorocarbons. Each 25-mL spray bottle contains 6.25 mg of flunisolide.

Fluocinonide Topical Solution

Lidex topical solution contains fluocinonide 0.5 mg/mL in a solution of alcohol (35%), citric acid, diisopropyl adipate, and propylene glycol. In this formulation, the active ingredient is totally in solution.

Fluorouracil Solution

Efudex solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropylcellulose, parabens (methyl and propyl), and disodium edetate.

Fluorouracil Topical Solution

Fluoroplex 1% topical solution contains fluorouracil 1%, propylene glycol, sodium hydroxide or hydrochloric acid to adjust the pH, and purified water.

Fluticasone Suspension Spray

MANUFACTURING DIRECTIONS

1. 2 g of fluticasone propionate and 0.02 g delta-tocopherol are weighed into a pressure-addition vessel.
2. After sealing and evacuation of the addition vessel, 1.5 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20˚C) in another pressure addition vessel is added with stirring.
3. The suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Furosemide Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	Furosemide, 5% excess	1.05
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1500.00	4	Sorbitol 70%	300.00
500.00	5	Glycerin	100.00
500.00	6	Propylene glycol	100.00
0.50	7	FD&C yellow no. 6	0.10
2.50	8	Orange flavor	0.50
q.s.	9	Sodium hydroxide	0.44
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 20% of item 10 to a suitable stainless steel-jacketed vessel.
2. Add items 2 and 3 and heat to 90˚ to 95˚C to dissolve. Cool to 40˚C after complete dissolution.
3. In a separate vessel, charge items 4, 5, and 6 and mix well.
4. Dissolve item 9 in a portion of item 10 in a separate vessel.
5. Add item 1 to step 4 and mix well.
6. In a separate vessel, dissolve item 7 in a portion of item 10.
7. Add to step 6.
8. Add step 2 to step 7.
9. Add item 8 and mix well.
10. Fill.

Gabapentin Oral Solution

Gabapentin solution contains 250 mg/5 mL of gabapentin. The inactive ingredients for the oral solution are glycerin, xylitol, purified water, and artificial cool strawberry anise flavor.

Galantamine Hydrobromide Oral Solution

Reminyl is available as a 4 mg/mL galantamine hydrobromide oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium saccharin, sodium hydroxide, and purified water.

Glucose, Fructose, and Phosphoric Acid Antiemetic Solution

Emetrol is an oral solution containing balanced amounts of dextrose (glucose) and levulose (fructose) and phosphoric acid with controlled hydrogen ion concentration. Available in original lemon-mint or cherry flavor. Each 5-mL teaspoonful contains dextrose (glucose), 1.87 g; levulose (fructose), 1.87 g; phosphoric acid, 21.5 mg; glycerin; methylparaben; purified water; D&C yellow no. 10; and natural lemon–mint flavor in lemon–mint Emetrol and FD&C red no. 40 and artificial cherry flavor in cherry Emetrol.

Gramicidin Opthalmic Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
130.00	1	Gramicidin	130.00
1.00	2	Cremophor RH 40	1.00
10.00	3	Alcohol	10.00
q.s.	4	Preservatives	q.s.
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable mixing and jacketed vessel; heat to 65°C and mix.
2. Cool to room temperature.
3. In a separate vessel, add and mix items 3 to 5.
4. Add to step 2. Mix and fill.

Guaifenesin, Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Guaifenesin	20.00
400.00	2	Sucrose	400.00
240.00	3	Glucose liquid	240.00
120.00	4	Sorbitol solution	120.00
3.00	5	Saccharin sodium powder dihydrate	3.00
2.50	6	Sodium benzoate powder	2.50
30.00	7	Psuedoephedrine hydrochloride	30.00
1.00	8	Carbinoxamine maleate	1.00
6.60	9	Chlophedianol hydrochloride	6.60
105.00	10	Dye red E123 (Amaranth)	105.00 mg
3.75	11	Dye blue FD&C no. 1	3.75 mg
q.s.	12	Acid hydrochloric	q.s.
50.00	13	Menthol crystals	50.0 mg
2.75	14	Flavors	2.75
65.00	15	Oil orange terpeneless no. 54125	65.00 mg
5.66	16	Alcohol 190 proof (10% ex)	5.66
0.52 g	17	Filter aid hyflo	0.52
420.0 g	18	Water, purified, distilled approximate	420.00

MANUFACTURING DIRECTIONS

1. Charge 260 mL purified water into a suitable tank.
2. Begin heating water to 70˚ to 80˚C while adding guaifenesin and sucrose with stirring.
3. Continue stirring to dissolve ingredients.
4. Remove heat; add glucose liquid and sorbitol to solution from step 3 with stirring.
5. Add saccharin sodium, sodium benzoate, pseudoephedrine hydrochloride, carbinoxamine maleate, and chlophedianol hydrochloride to solution from step 4. Stir well to dissolve all ingredients.
6. Dissolve dye red E123 and FD&C no. 1 in 10 mL warm, purified water.
7. Add dye solution to solution from step 6 with stirring. Cool solution to 30˚ to 35˚C.
8. q.s. to 975 mL using purified water; mix well.
9. Adjust to pH 4.25 (range 4 to 4.5) with hydrochloric acid (ca. 0.65 g/L of drops).
10. Stir well after each addition of acid. Dissolve menthol, flavors, and orange oil in alcohol; add mixture to solution from step above with good stirring.
11. Stir the solution slowly for 2 hours.
12. Allow to stand overnight to cool and remove entrapped air.
13. q.s. to 1 L with purified water; stir well.
14. Add filter aid hyflo to solution and mix well.
15. Recirculate through filter press or equivalent until sparkling clean.

Haloperiodol Oral Liquid

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.00	1	Haloperiodol	2.00
11.00	2	Lactic acid	11.00
0.20	3	Propyl paraben	0.20
1.90	4	Methyl paraben	1.90
q.s.	5	Sodium hydroxide for pH adjustment, approximate	0.24
q.s.	6	Water, purified, approximate	990 mL
q.s.	7	Nitrogen gas	q.s.
q.s.	8	Lactic acid	q.s.

MANUFACTURING DIRECTIONS

1. Charge approximately 700 mL of water into a suitable mixing tank. Add and dissolve lactic acid with stirring; while mixing, add haloperiodol. Mix until complete solution (approximately 15 minutes).
2. Charge 240 mL of water into a separate container and heat to boiling. Add and dissolve methyl and propyl parabens. Mix until complete solution. Add this solution to step 1 solution.
3. Check pH. If necessary, adjust to pH 2.75 (range 2.5 to 3) with 2% sodium hydroxide. Continue mixing for 10 minutes after addition of sodium hydroxide. Record pH and amount of sodium hydroxide added. Lactic acid (#8) may also be used to adjust pH.
4. q.s. to 1 L with water and mix well.
5. Filter solution through 8-micron membrane filter (or similar) into a suitable container, under nitrogen protection.
6. Fill under nitrogen.

Heparin Nasal Spray

Charge 5 g of heparin into a pressure-addition vessel and suspend with stirring 50 g of ethanol in which 0.25 g of lecithin have previously been dissolved. After sealing and evacuation thereof, 1.5 kg of HFA 227 that has previously been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel is added with stirring and homogenized. The suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Hydrocodone Bitartarate Elixir

Each 5 mL contains hydrocodone bitartarate 2.5 mg, acetaminophen 167 mg, and 7% alcohol. In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, methylparaben, propylene glycol, propylparaben, purified water, saccharin sodium, sorbitol solution, sucrose, and D&C yellow no. 10 and FD&C yellow no. 6 as coloring and natural and artificial flavoring.

Hydrocodone Polistirex Extended-Release Suspension

Each teaspoonful (5 mL) of TUSSIONEX Pennkinetic extended-release suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. TUSSIONEX Pennkinetic extended-release suspension provides up to 12-hour relief per dose. Hydrocodone is a centrally acting narcotic antitussive. Chlorpheniramine is an antihistamine. TUSSIONEX Pennkinetic extended-release suspension is for oral use only. Hydrocodone polistirex: sulfonated styrene-divinylbenzene copolymer complex with 4,5(alpha)- epoxy-3-methoxy-17-methylmorphinan-6-one. Chlorpheniramine polistirex: sulfonated styrene-divinylbenzene copolymer complex with 2-[p-chloro-(alpha)-[2-(dimethylamino) ethyl]-benzyl]pyridine. Inactive ingredients: ascorbic acid, D&C yellow no. 10, ethylcellulose, FD&C yellow no. 6, flavor, high fructose corn syrup, methylparaben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propylparaben, purified water, sucrose, vegetable oil, and xanthan gum.

Hydromorphone Hydrochloride Oral Liquid

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a narcotic analgesic. Each 5 mL (1 teaspoon) contains 5 mg of hydromorphone hydrochloride. In addition, other ingredients include purified water, methylparaben, propylparaben, sucrose, and glycerin. It may contain traces of sodium bisulfite.

Hydroxyzine Pamoate Oral Suspension

Hydroxyzine pamoate is designated chemically as 1-(p-chlorobenzhydryl)4-[2-(2-hydroxyethoxy) ethyl] diethylenediamine salt of 1,1′-methylene bis (2 hydroxy-3-naphthalene carboxylic acid). Hydroxyzine pamoate 25 mg/5 mL; inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, lemon flavor, propylene glycol, sorbic acid, sorbitol solution, and water.

Hyoscine Butylbromide Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	Hyoscine butylbromide	1.00
3300.00	2	Sugar	660.00
5.00	3	Methyl paraben	1.00
1.50	4	Propyl paraben	0.30
962.50	5	Sorbitol 70%	19.30
10.00	6	Sodium saccharin	2.00
35.00	7	Sodium chloride	7.00
0.70	8	Citric acid monohydrate	0.14
0.75	9	Sodium citrate	0.15
10.00	10	Flavor	2.00
5.00	11	Flavor	1.00
5.00	12	Flavor	1.00
q.s.	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. In a suitable stainless steel container charge 300 mL item 13 and heat to 90˚ to 95˚C.
2. Add and dissolve items 3 and 4.
3. Add item 2 and dissolve.
4. Add item 5 and dissolve. Cool to room temperature
5. In 10 mL item 13, add and dissolve items 6 and 7 and add to step 4.
6. In 10 mL item 13, add and dissolve item 8 and add to step 4.
7. In 10 mL item 13, add and dissolve item 7 and add to step 4.
8. In 20 mL item 13, add and dissolve item 1 and add to step 4.
9. Add flavors.
10. Make up volume and fill.

Hyoscyamine Sulfate Elixir

LEVSIN elixir contains 0.125 mg hyoscyamine sulfate per 5 mL with 20% alcohol for oral administration. LEVSIN elixir also contains, as inactive ingredients, FD&C red no. 40, FD&C yellow no. 6, flavor, glycerin, purified water, sorbitol solution, and sucrose.

Ibuprofen Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (pluronic P105 63.16%, ethanol 18.95%, water 17.89%)	q.s. to 1 L
50.00	2	Ibuprofen	50.00

MANUFACTURING DIRECTIONS

1. Screen the ibuprofen to reduce the particle size.
2. Add the ibuprofen into a clean vessel.
3. Add ethanol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Ibuprofen Pediatric Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.00	1	Ibuprofen low density (100% particle size below 50 microns, tapped density is 0.3 g/mL to 0.4 g/mL)	20.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
5.00	4	Saccharin sodium	1.00
5.00	5	Edatate disodium (sodium EDTA)	1.00
500.00	6	Glycerin (glycerol)	100.00
500.00	7	Sorbitol (70% solution)	100.00
10.00	8	Xanthan gum (Keltrol-F)	2.00
20.00	9	Microcrystalline cellulose (Avicel RC 591)	4.00
5.00	10	Polysorbate 80 (Tween 80)	1.00
8.50	11	Citric Acid	1.70
1.35	12	FD&C red no. 40	0.27
7.50	13	Mixed fruits flavor	1.50
5.00	14	Strawberry flavor	1.00
—	15	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat 302.0 g of item 15 to 90˚C and dissolve item 2 while mixing in mixer.
2. Cool to about 50˚C.
3. Add items 3, 5, 4, 11, and 7 to mixer while mixing and dissolve.
4. Filter the syrup through Seitz Supra 2600 filters in clean stainless steel tank.
5. In a clean stainless steel vessel dissolve item 10 in 35.0 g of item 15 (40˚C).
6. Add item 1 slowly while mixing with stirrer.
7. Mix for 30 minutes to make uniform dispersion. Avoid excessive foaming.
8. Disperse items 8 and 9 in item 6 in a clean and dry stainless steel container using stirrer. Add 75.0 g of hot item 15 (70˚ to 90˚C) at once while mixing.
9. Mix for 20 minutes to make homogeneous smooth mucilage.
10. Add about 500 g syrup, ibuprofen dispersion, and mucilage to the mixer.
11. Rinse the containers of ibuprofen dispersion and mucilage with 50.0 g of item 15 (40˚C).
12. Add the rinsings to the mixer. Set the mixer: temperature, 25˚C; mixer speed, 18 rpm; manual mode vacuum, 0.5 bar.
13. Mix for 3 minutes at low homogenizer speed.
14. Mix for 2 minutes at homogenizer high speed. Check the suspension for uniformity of dispersion.
15. Homogenize for additional 3 minutes at high speed, if required.
16. Add the balance syrup about 507.6 g from step above to the mixer.
17. In a separate container dissolve item 12 in 6.0 g of cooled item 15 (40˚C) and transfer to the mixer.
18. Add the items 13 and 14 to the mixer. Set the mixer: temperature, 25˚C; mixer speed, 18 rpm; manual mode vacuum, 0.5 bar. Mix for 15 minutes.
19. Mix for 5 minutes at homogenizer low speed.
20. Mix for 5 minutes at homogenizer high speed.
21. Check the suspension for uniformity.
22. Adjust the final volume to 1 L by using purified water.

Ibuprofen Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Ibuprofen	20.00
200.00	2	Cremophor RH 40	200.00
q.s.	3	Preservatives	q.s.
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. In a suitable stainless steel-jacketed vessel, add and suspend item 1 in item 2 by heating it to 60˚C.
2. In a separate vessel, add items 3 and 4 and heat to 90˚ to 95˚C to dissolve preservatives, add to step 1.
3. Mix and fill.

Ibuprofen Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40.00	1	Ibuprofen	40.00
250.00	2	Sucrose	250.00
80.00	3	Kollidon CL-M	80.00
20.00	4	Kollidon 90F	20.00
20.00	5	Sodium citrate	20.00
q.s.	6	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 2 and 4 to 6 (40%) in a suitable mixer.
2. Add and suspend item 3.
3. Add and disperse item 1. Homogenize if necessary.
4. Bring to volume with item 6. Mix and fill.

Ibuprofen Suspension, Sugar Free

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40.00	1	Ibuprofen	40.00
10.00	2	Cremphor RH 40	100.00
50.00	3	Lutron F 68	50.00
q.s.	4	Preservatives	q.s.
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve Lutrol F 68 and the preservatives in purified water.
2. In a separate vessel add and mix items 1 and 2.
3. Add to step 1.
4. Homogenize if necessary.
5. Bring to volume with item 5. Mix and fill.

Insulin Inhalation Spray

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Insulin	10.00
9.00	2	Brij 98	9.00
10.00	3	Sodium lauryl sulfate	10.00
200.00	4	Alcohol, anhydrous	200.00
q.s.	5	HFA 134a (1,1,1,2-tetrafluoroethane)	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Weigh insulin in a clean glass container and dissolve in acid buffer and titrate to a pH of 7 with Tris buffer.
2. Add Brij 98 and sodium lauryl sulfate to the insulin solution to form a homogenous solution.
3. Lyophilize and suspend dried particles in a non-aqueous suspension medium of ethanol and then charge with hydrofluoroalkane (HFA) 134a.
4. Fill the formulation in a pressure-resistant container fitted with a metering valve.

Ipratropium Bromide Inhalation Solution

Atrovent inhalation solution is administered by oral inhalation with the aid of a nebulizer. It contains ipratropium bromide 0.02% (anhydrous basis) in a sterile, isotonic saline solution, pH adjusted to 3.4 (3 to 4) with hydrochloric acid.

Ipratropium Bromide Nasal Spray

Atrovent (ipratropium bromide) Nasal Spray 0.03% is a metered-dose, manual-pump spray unit that delivers 21 mcg (70 μL) ipratropium bromide per spray on an anhydrous basis in an isotonic, aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, edetate disodium, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 or 345 sprays.

MANUFACTURING DIRECTIONS

1. 2.25 g of micronized ipratropium bromide and 11.25 g of micronized salbutamol are weighed into a pressure-addition vessel.
2. After sealing and evacuation thereof, 10.5 kg of HFA 227 that has previously been aerated with carbon dioxide and adjusted to a pressure of 6.25 bar (20°C) in another pressure addition vessel is added.
3. After homogenization of this mixture, the suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Iron Infant Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.18	1	Propyl paraben	0.180
0.02 2	2	Methyl paraben	0.020
1000.00	3	Sorbitol solution	1.000 kg
4.00	4	Acid citric powder hydrous	4.000
125.00	5	Iron sulfate	125.000
0.10 6	6	Sodium metabisulfite	0.100
0.50	7	Flavor guarana artificial	0.500
20.00	8	Alcohol (ethanol)	900.14
0.140	9	Dye	0.140
q.s	10	Sodium hydroxide	q.s.
q.s	11	Acid citric powder	1 q.s.
q.s	12	Water, purified	q.s. to 1 L
q.s	13	Filter aid hyflo	1.000
q.s.	14	Nitrogen liquid or	q.s.
q.s.	15	Carbon dioxide gas	q.s.

MANUFACTURING DIRECTIONS

The product is susceptible to oxidation. Protect from atmospheric air all the time using carbon dioxide or nitrogen. The product must be manufactured and held in glass-lined or stainless steel tanks. Product waiting to be filled should either be in a closed tank with a CO_2 atmosphere or in an open tank covered with polyethylene sheeting taped tightly that constantly has a slow stream of CO_2 gas flow into the tank headspace. Avoid vortex formation throughout processing.

1. Charge 144 mL of purified water into a mixing tank.
2. Heat to 95° to 100°C and add parabens with strong agitation.
3. Add sorbitol solution and citric acid (item 4) while mixing.
4. Bring solution to 90°C while mixing.
5. Cool the solution while mixing to 60° to 65°C and hold at this temperature with CO_2 or nitrogen gas bubbling into it. CO_2 gas protection is continued for the remainder of the manufacturing process.
6. Add ferrous sulfate and dissolve while mixing, holding at 60° to 65°C. Cool to 25°C with mixing. Add sodium metabisulfite and dissolve while mixing.
7. Avoid vortex formation. Dissolve dye in 2 mL freshly boiled purified water, and add to the tank. Mix. Dissolve the guarana flavor in alcohol, add to the tank, and mix.
8. Check pH (range: 1.8 to 2.2). Adjust, if necessary, with a solution of 10% sodium hydroxide or a solution of 10% citric acid.
9. Make up to volume with freshly boiled purified water and mix.
10. Readjust to volume if necessary with freshly boiled purified water and mix.
11. Add hyflo filter aid and mix. Filter through press until clear.
12. Bubble CO_2 or nitrogen gas into clear filtrate for 5 minutes. Then seal tank and hold product under CO_2 or nitrogen protection.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
125.00	1	Glycerin	125.0
1.40	2	Methyl paraben	1.40
0.16	3	Propyl paraben	0.16
79.61	4	Sorbitol solution	364.33
3.30	5	Xanthan gum	3.30
10.00	6	Sucrose	100.00
0.20	7	Saccharin	2.00
105.00	8	Elemental iron USE iron polystyrene sulfonate	530.31
50.00	9	Acid ascorbic, 35% excess	61.950
0.10 v/v	10	Flavor	1.0 mL
0.10 v/v	11	Flavor guarana artificial	1.0 mL
q.s.	12	Sodium hydroxide	12. 1.0
q.s.	13	Dye	2.0
9.50	14	Water, purified	95 mL
10.00	15	Sorbitol solution, approximate	10.0

MANUFACTURING DIRECTIONS

1. Add glycerin (item 1) to the tank. Commence heating with agitation.
2. Add and disperse parabens. Continue heating to 70˚ to 80˚C and mix until solution is complete.
3. Force cool to 30˚C then add and disperse xanthan gum (item 5).
4. Add sorbitol solution (item 4) and 80 mL of purified water (item 14) and heat with mixing to 60˚ to 70˚C until the xanthan gum is fully dissolved.
5. Add and disperse saccharin and sugar (items 7 and 6).
6. Mix at 60˚ to 70˚C until dispersion is complete.
7. Force cool to 25˚ to 30˚C with continuous mixing.
8. Commence N_2 gas protection and maintain for the remainder of the manufacturing process.
9. Add and disperse ascorbic acid. Continue mixing for 30 minutes at 25˚ to 30˚C. Use suitable stainless steel high-powered stirrer.
10. Mix the iron polystyrene sulfonate milled slurry, in the original epoxy lined drums, under N_2 gas protection until uniform.
11. Add the slurry to the main batch and mix for 30 minutes at 25˚ to 30˚C. Avoid scraping the epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry.
12. Add and disperse the flavors. Mix well.
13. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a pH of 3 (range 2.8 to 3.2).
14. Dissolve the dye in 5 to 7 mL of water at 40˚ to 45˚C by stirring for 10 minutes.
15. Add this solution to the main batch through a 420-micron-aperture screen with mixing.
16. Rinse container with 2 to 3 mL water at 40˚ to 45˚C, and add to bulk through a 420-micron screen.
17. Continue to mix under vacuum until uniform.
18. Pass suspension through the colloid mill at a gap setting of 100 to 150 micrometers.
19. Adjust flow rate such that the temperature rise of the suspension does not exceed 10˚C.
20. Collect the milled suspension in a stainless steel-jacketed tank with vacuum. Mix at 25˚ to 30˚C under vacuum until a uniform suspension is achieved.
21. Flush the bulk suspension with N_2 and seal. Hold at 25˚ to 30˚C.

Isoproterenol Sulfate and Calcium Iodide Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.569	1	Glucose liquid	311.60
269.50	2	Glycerin	53.90
150.00	3	Calcium iodide anhydrous, USE calcium iodide solution 27%	111.11
5.00	4	Ascorbic acid	1.00
2.428	5	Sucrose	485.30
4.00	6	Saccharin sodium	0.80
5.00	7	Sodium cyclamate	1.00
6.55	8	Flavor honey	1.31
1.66	9	Flavor mint	0.33
0.26	10	Alcohol 190 proof	51.53
3.00	11	Isoproterenol sulfate	0.60
0.25	12	Dye yellow	0.05
1.25	13	Caramel	0.25
q.s.	14	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge in a stainless steel tank items 1, 2, 5, 6, 7, 10, and 90% of item 14. Mix well; heat if necessary.
2. In a separate vessel add an dissolve items 4, 8, 9, 12, and 13 in item 14; mix well and add to step 1.
3. Add remaining items, mix, bring to volume. Fill.

Isotretinoin Capsules

Isotretinoin, a retinoid, is available as in 10-mg, 20-mg, and 40-mg soft gelatin capsules for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg, iron oxide (red) and titanium dioxide; 20 mg, FD&C red no. 3, FD&C blue no. 1, and titanium dioxide; 40 mg, FD&C yellow no. 6, D&C yellow no. 10, and titanium dioxide. Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow-orange to orange crystalline powder with a molecular weight of 300.44.

Itraconazole Oral Solution

Itraconazole oral solution contains 10 mg of itraconazole per milliliter, solubilized by hydroxypropyl-(beta)-cyclodextrin (400 mg/mL) as a molecular inclusion complex. The solution is clear and yellowish in color with a target pH of 2. Other ingredients are hydrochloric acid, propylene glycol, purified water, sodium hydroxide, sodium saccharin, sorbitol, cherry flavor 1, cherry flavor 2, and caramel flavor.

Kaolin, Pectin, and Aluminum Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
147.60	1	Sodium methyl paraben	4.92
6.72	2	Sodium propyl paraben	0.22
36.00	3	Magnesium aluminum silicate Type IA (Veegum)	1.20
486.60	4	Kaolin powder	0.19
43.40	5	Pectin	4.33
120.00	6	Sodium CMC premium low viscosity	4.00
210.00	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium	0.70
15.37	9	Flavor	0.51
1.23	10	Flavor	0.041
q.s.	11	Water, purified, distilled	q.s.
q.s.	12	Acid citric anhydrous powder	q.s.
63.30	13	Aluminum hydroxide	12.72

MANUFACTURING DIRECTIONS

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add the methylparaben and propylparaben to the tank and heat to 90˚ to 95˚C.
3. Cool to 70˚C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70˚C.
5. Add kaolin with constant mixing at 70˚C until evenly dispersed.
6. Add pectin and mix for 2 hours, maintaining the temperature of 70˚C.
7. Add the sodium CMC premium low viscosity and mix for at least 30 minutes, maintaining the temperature at 70˚C. Cool to 60˚C and hold at this temperature.
8. Add aluminum hydroxide gel and mix under vacuum.
9. Add in order cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes. While mixing, cool to room temperature and allow standing overnight to hydrate.
10. After overnight standing (minimum 12 hours), mix for 30 minutes.
11. Add and mix flavors. Check and record pH (range 4.5 to 7.5). If pH is above 7.5, adjust with a 60% solution of citric acid to the desired pH.
12. Add water to 1 L and mix thoroughly for 3 hours.
13. Strain product through muslin cloth into holding tanks and cover.

Kaolin–Pectin Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L, g**
147.60	1	Sodium methyl paraben	4.92
6.72	2	Sodium propyl paraben	0.224
36.00	3	Magnesium aluminum silicate Type IA (Veegum)	1.20
5.832 g	4	Kaolin powder	194.40
130.00	5	Pectin	4.33
120.00	6	Sodium CMC premium low viscosity	4.00
210.00	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium powder	0.70
15.37	9	Flavor	0.51
1.23	10	Flavor	41.13
q.s.	11	Water, purified approximate	q.s.
q.s.	12	Acid citric anhydrous powder	q.s.

MANUFACTURING DIRECTIONS

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add the methylparaben and propylparaben to the tank and heat to 90° to 95°C.
3. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70°C.
5. Add kaolin with constant mixing at 70°C until evenly dispersed.
6. Add pectin and mix for 2 hours, maintaining the temperature of 70°C.
7. Add the sodium CMC premium low viscosity and mix for at least 30 minutes, maintaining the temperature at 70°C.
8. Cool to 60°C and hold at this temperature. Add in order cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes.
9. While mixing, cool to room temperature and allow standing overnight to hydrate. After overnight standing (minimum 12 hours), mix for 30 minutes.
10. Mix while adding the flavors.
11. Check and record pH (range 4.5 to 7.5). If pH is above 7.5, adjust with a 60% solution of citric acid to the desired pH.
12. Add water to 1 L and mix thoroughly for 3 hours. Strain product through muslin cloth into holding tanks and cover.

Ketoprofen Topical Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (pluronic F 127 56.12%, ethanol 30.61, water 13.27%)	q.s. to 1 L
20.00	2	Ketoprofen	20.00
q.s.	3	Perfumes	q.s.

MANUFACTURING DIRECTIONS

1. Screen the ketoprofen to reduce the particle size.
2. Add the ketoprofen into a clean vessel.
3. Add ethanol to the vessel.
4. Subsequently add poloxamer and water to the vessel.
5. Mix until uniform.

Ketotifen Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.20	1	Ketotifen hydrogen fumarate	0.27
0.10	2	Flavor	0.10
0.17	3	Propyl paraben	0.17
0.33	4	Methyl paraben	0.33
2.10	5	Citric acid anhydrous	2.10
3.20	6	Disodium hydrogen phosphate anhydrous	3.20
20.00	7	Ethanol	20.00
300.00	8	Sucrose	300.00
350.00	9	Sorbitol	350.00
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Take 1.5 L of purified water and heat to 90° to 95°C, allow to cool down to 30°C, and bubble with nitrogen gas. Keep for batch preparation.
2. Dissolve the parabens in 1 L in a separate vessel and stir until the solution is completely clear. Add citric acid, disodium hydrogen phosphate anhydrous, sucrose, and sorbitol and stir slowly to dissolve until clear solution is obtained. Cool to room temperature.
3. In a separate container dissolve ketotifen hydrogen fumarate in ethanol until clear.
4. Add the flavor to the alcoholic solution of ketotifen and dissolve.
5. Add the alcoholic mixture slowly to the syrup while stirring at room temperature avoiding entrapment of air.
6. Pass the syrup through 100-mesh screen and then through filter press until sparkling clear.

Lamivudine Oral Solution

Epivir oral solution is for oral administration. One milliliter (1 mL) of Epivir oral solution contains 10 mg lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose.

One milliliter (1 mL) of Epivir-HBV oral solution contains 5 mg of lamivudine (5 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose.

Levalbuterol Hydrochloride Inhalation Solution

Xopenex (levalbuterol HCl) inhalation solution is supplied in unit-dose vials and requires no dilution before administration by nebulization. Each 3-mL unit-dose vial contains either 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and sulfuric acid to adjust the pH to 4.0 (3.3 to 4.5).

Levocarnitine Oral Solution

Each 118-mL container of Carnitor (levocarnitine) oral solution contains 1 g of levocarnitine/10 mL. It also contains artificial cherry flavor, D,L-malic acid, purified water, and sucrose syrup. Methylparaben and propylparaben are added as preservatives. The pH is approximately 5.

Linezolid for Oral Suspension

Zyvox for oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors.

Lithium Carbonate Solution

Each 5 mL of syrup for oral administration contains Lithium ion (Li +) 8 mEq (equivalent to amount of lithium in 300 mg of lithium carbonate), alcohol 0.3% v/v.

Lithium Citrate Syrup

Each 5 mL of syrup for oral administration contains lithium ion 8 mEq (equivalent to amount of lithium in 300 mg of lithium carbonate), alcohol 0.3% v/v. Lithium citrate syrup is a palatable oral dosage form of lithium ion. Lithium citrate is prepared in solution from lithium hydroxide and citric acid in a ratio approximately dilithium citrate.

Lomustine Nasal Spray

Charge 112.5 g of micronized lomustine into a pressure-addition vessel. After sealing and evacuation thereof, 10.5 kg of HFA 227 that has been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel in which 312 g of ethanol has been initially introduced is added. After homogenization of this mixture, the formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Loracarbef for Oral Suspension

After reconstitution, each 5 mL of lorabid for oral suspension contains loracarbef equivalent to 100 mg (0.286 mmol) or 200 mg (0.57 mmol) anhydrous loracarbef activity. The suspensions also contain cellulose, FD&C red no. 40, flavors, methylparaben, propylparaben, simethicone emulsion, sodium carboxymethylcellulose, sucrose, and xanthan gum.

Loratidine Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
5.00	1	Loratadine	1.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
2.50	4	Saccharin sodium	0.50
12.50	5	Citric acid (monohydrate)	2.50
250.00	6	Glycerin (glycerol)	50.00
765.00	7	Propylene glycol	153.00
6.87	8	Hydrochloric acid 37% (concentrated)	1.51
6.25	9	All fruit flavor	1.25
1.50	10	Raspberry flavor	0.30
—	11	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

Hydrochloric acid (concentrated) is very corrosive. Care should be taken during handling. Rubber gloves and protective goggles should be worn during dispensing and manufacturing.

1. Add 380.0 g of item 11 to a stainless steel manufacturing vessel and heat to 90° to 95°C.
2. Add item 2 while mixing at slow speed at a temperature of 90° to 95°C. Cool to 50°C.
3. Add items 3, 4, 5, and 6 in order while mixing at low speed at 50°C. Mix for 15 minutes at low speed. Cool to 30°C.
4. Take 13.53 g of item 11 in a stainless steel container. Add item 8 carefully. Add hydrochloric acid solution quantity 13.675 g to the manufacturing vessel. Adjust the pH between 2.3 and 2.4. If required, add the additional quantity and record. Discard the remaining quantity. Mix for 5 minutes.
5. Dissolve item 1 in 145.0 g of item 7 in a stainless steel drum while stirring. Add to the manufacturing vessel.
6. Rinse the stainless steel drum with 8.0 g of item 7. Transfer to manufacturing vessel.
7. Add items 9 and 10 in to manufacturing vessel. Mix for 5 minutes at low speed.
8. Make up the volume to 1 L with item 11.
9. Filter and fill.

Mafenide Acetate Topical Solution

Sulfamylon for 5% topical solution is provided in packets containing 50 g of sterile mafenide acetate to be reconstituted in 1000 mL of sterile water for irrigation or 0.9% sodium chloride irrigation. After mixing, the solution contains 5% w/v of mafenide acetate. The solution is an antimicrobial preparation suitable for topical administration.

Magaldrate Instant Powder for Dry Syrup

Bill of Materials			
Scale (mg/sachet)	**Item**	**Material Name**	**Quantity/1000 Sachets (g)**
800.00	1	Magaldrate	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol, crystalline	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
q.s.	9	Water	about 280 mL

MANUFACTURING DIRECTIONS

1. Granulate mixture 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-mL flask. Instant granules in sachets: suspend 2 g (1 sachet) in a glass of water (800 mg magaldrate).

Magaldrate Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/1000 Tablets (g)**
100.00	1	Magaldrate	100.00
80.00	2	Kollidon CL-M	80.00
20.00	3	Kollidon 90 F	20.00
10.00	4	Orange flavor	10.00
0.50	5	Coconut flavor	0.50
0.80	6	Banana flavor	0.80
0.20	7	Saccharine sodium	0.20
q.s.	8	Preservatives	q.s.
q.s.	9	Water	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve or suspend all the solids in water under aseptic conditions.
2. Adjust pH to about 9.00.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Water, purified	q.s. to 1 L
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Acid benzoic	1.00
3.75	5	Saccharin sodium powder dihydrate	0.75
2.00 g	6	Magaldrate wet cake (18 to 20%)	400.00
1.00 g	7	Sorbitol solution	260.00
12.50	8	Silicon dioxide colloidal (international)	2.50
q.s.	9	Acid citric powder hydrous	q.s.
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.000 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

MANUFACTURING DIRECTIONS

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm), made with freshly boiled and cooled town water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled purified water should be used for rinsing.

1. Charge 285 mL purified water into a suitable jacketed tank and heat to 90˚ to 95˚C.
2. Add and dissolve parabens, acid benzoic, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85˚ to 90˚C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well. (Adjust the speed of agitator and of the homogenizer to ensure effective mixing and to maintain free mobility of the suspension.)
4. Add sorbitol solution and mix well. Raise the temperature, if necessary, maintaining temperature at 85˚ to 90˚C.
5. Add, in small quantities, the remaining half of magaldrate cake or powder and disperse well. Mix for 1 hour and then remove heat. (Adjust the speed of the agitator and of the homogenizer to maintain the mobility of suspension.)
6. Separately blend silicon dioxide colloidal with xanthan gum and disperse the blend in glycerin, with constant mixing.
7. While maintaining temperature at 85˚ to 95˚C, add and disperse the suspension from previous step to the main tank and mix well. Avoid lump formation at any stage. Cool to room temperature.
8. Add dimethyl polysiloxane emulsion and mix well.
9. Add flavor and mix well. Dissolve acid citric in twice the quantity of purified water, and adjust pH if necessary. Check and record pH (range 7.5 to 8).
10. Add purified water to volume and mix well, for a minimum of 30 minutes.
11. Filter through a 180-micron aperture nylon cloth and store in a suitable tank.

Mebendazole Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
102.00	1	Mebendazole[a]	20.40
10.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	0.20
750.00	4	Propylene glycol	150.00
8.25	5	Sodium citrate	1.65
7.50	6	Saccharin sodium	1.50
0.55	7	Citric acid (monohydrate)	0.11
52.50	8	Microcrystalline cellulose	10.50
25.00	9	Carboxymethylcellulose sodium	5.00
7.50	10	Polysorbate 80	1.50
12.50	11	All fruits flavor	2.50
—	12	Water, purified	q.s. to 1 L

[a]2 mg/5 mL mebendazole added as an extra to compensate the loss on drying and assay of the material.

MANUFACTURING DIRECTIONS

1. Load 300.0 g of item 12 (25˚ to 30˚C) in mixer. In it dissolve items 5, 7, and 6 while stirring at a speed of 18 rpm.
2. Dissolve items 2 and 3 in 30.0 g of item 4 (45˚C) in a stainless steel container while stirring by stirrer.
3. Cool to 25˚ to 30˚C.
4. Add the paraben solution into step 1 while mixing.
5. Disperse item 8 in 200.0 g of item 12 (25˚ to 30˚C) in a stainless steel container while stirring by stirrer. Keep aside for 1 hour for complete hydration.
6. Disperse item 9 in 100.0 g of item 12 (70˚C) in a stainless steel container while stirring by stirrer.
7. Cool to 25˚ to 30˚C. Keep aside for 1 hour for complete gelation. Cooling is necessary for gelation.
8. Dissolve item 10 in 20.0 g of item 12 (50˚C) in a stainless steel container while stirring by stirrer.
9. Cool to 30˚C. Add 120.0 g of item 4 while mixing.
10. Disperse item 1 while mixing. Keep aside for complete levigation.
11. Add the avicel dispersion and sodium CMC dispersion from step 3 and step 4 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
12. Add the mebendazole dispersion from step 5 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
13. Add all item 11 into step 6. Make up the volume up to 1 L with item 12. Mix at a speed of 18 rpm for 5 minutes.
14. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to stainless steel storage tank, previously sanitized by 70% ethanol.

Mebendazole Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Mebendazole	20.00
30.00	2	Lutrol F 127	30.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
q.s.	5	Water, purified	q.s.

MANUFACTURING DIRECTIONS

1. Charge 80% of item 5 in a stainless steel-jacketed vessel, heat to 90˚ to 95˚C.
2. Add items 3 and 4 and stir to dissolve.
3. Cool to 40˚C and add item 2, stir to dissolve completely.
4. Add item 1 and mix well. Homogenize if necessary.

Megestrol Acetate Oral Suspension

MEGACE oral suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per milliliter. MEGACE oral suspension contains the following inactive ingredients: alcohol (maximum of 0.06% v/v from flavor), citric acid, lemon–lime flavor, polyethylene glycol, polysorbate 80, purified water, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40.00	1	Megestrol acetate	40.00
100.00	2	Glycerin	100.00
100.00	3	Sorbitol	100.00
0.30	4	Polysorbate 90	0.30
2.20	5	Xanthan gum	2.20
2.00	6	Sodium benzoate	2.00
0.60	7	Sodium citrate	0.60
50.00	8	Sucrose	50.00
0.80	9	Lemon flavor	0.80
q.s.	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge glycerol, sorbitol, and polysorbate in a suitable container. Mix well.
2. Charge xanthan gum in a separate vessel with item 10 and allow overnight hydration.
3. Add sodium citrates, sucrose, sodium benzoate, and flavor to step 1 and then add step 2 to step 1.
4. Pass the gum slurry through a screen.
5. Add megestrol acetate and pass then suspension through a colloid mill or homogenizer to provide a uniform oral suspension.

Menthol and Benzocaine Solution

Bill of Materials			
Scale (mg/mg)	**Item**	**Material Name**	**Quantity/kg (g)**
q.s.	1	Vehicle (pluronic F 108 56.79%, ethanol 21.69%, water 21.52%)	q.s. to 1 kg
10.00	2	Menthol	10.00
20.00	3	Benzocaine	20.00
0.05	4	Eucalyptus oil	0.05
1.00	5	Sodium saccharin	1.00
0.50	6	Monoammonium glycerhizzinate	0.50
q.s.	7	Flavors and colors	q.s.

MANUFACTURING DIRECTIONS

1. Mill and screen the menthol and benzocaine to reduce the product particle size.
2. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycerizzinate into a clean vessel.
3. Add eucalyptus oil and ethanol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Menthol	10.00
10.00	2	Eucalyptus oil	10.00
40.00	3	Cremophor RH 40	40.00
4.50	4	Saccharin sodium	4.50
2.00	5	Sodium citrate	2.00
5.00	6	Citric acid	5.00
50.00	7	Lutrol F 127	50.00
67.00	8	Ethanol 96%	67.00
q.s.	9	Sicovit colorant	q.s.
801.00	10	Water	801.00

MANUFACTURING DIRECTIONS

1. Mix components 1 to 3 and heat to about 60°C.
2. Prepare solution of items 4 to 10, heat to about 60°C, and add it slowly to the well-stirred mixture of items 1 to 3.
3. Clear, colored liquids having a fresh mint taste are the desired result.

Mesalamine Rectal Suspension Enema

The active ingredient in the rectal suspension enema, a disposable (60 mL) unit, is mesalamine, also known as 5-aminosalicylic acid. Each rectal suspension enema unit contains 4 g of mesalamine. In addition to mesalamine, the preparation contains the inactive ingredients carbomer 934P, edetate disodium, potassium acetate, potassium metabisulfite, purified water, and xanthan gum. Sodium benzoate is added as a preservative. The disposable unit consists of an applicator tip protected by a polyethylene cover and lubricated with white petrolatum. The unit has a one-way valve to prevent back-flow of the dispensed product.

Mesalamine Rectal Suspension

Each rectal suspension enema unit contains 4 g of mesalamine. In addition to mesalamine, the preparation contains the inactive ingredients carbomer 934P, edetate disodium, potassium acetate, potassium metabisulfite, purified water, and xanthan gum. Sodium benzoate is added as a preservative.

Metformin Liquid

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.00	1	Metformin hydrochloride	100.00
400.00	2	Xylitol	400.00
5.00	3	Potassium bicarbonate	5.00
1.20	4	Potassium sorbate	1.20
2.75	5	Sodium saccharin	2.75
0.004 mL	6	Hydrochloric acid	4.00 mL
2.75	7	Wild cherry flavor	2.75
q.s.	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Under continuous stirring, add potassium bicarbonate and metformin hydrochloride to purified water and dissolve to get a clear solution.
2. Add hydrochloric acid solution as a dilute solution (approximately 1 molar) to the mixture of the previous step. This results in carbon dioxide gas formation (effervescent gas).
3. Add xylitol at a temperature of not more than 31°C and stir to get a clear solution.
4. Continue stirring and add artificial cherry flavor and saccharin.
5. Adjust the pH to a range of 4.6 to 4.9 using dilute solution of hydrochloric acid (if required).
6. Make up the volume and filter through clarifying grade filter, and fill in approved container.

Metoclopramide Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
4.00	1	Metoclopramide HCl, 10% excess	4.40
0.76	2	Saccharin sodium	0.76
1.00	3	Sorbic Acid	1.00
1.48	4	Sodium metabisulfite (sodium disufite)	1.48
0.10	5	Polyoxyl 35 castor oil (Cremophor EL)	0.10
5.20	6	Sodium citrate	5.20
8.52	7	Citric acid (monohydrate)	8.52
—	8	Water, purified	q.s. to 1L

MANUFACTURING DIRECTIONS

1. Load 80 g of item 8 to the mixer and heat to 90° to 95°C.
2. Dissolve items 2 and 3 while stirring. Mix for 15 minutes at high speed to get clear solution.
3. Cool the temperature to 25°C.
4. Transfer the solution to drops manufacturing vessel.
5. Add item 5 to the drops manufacturing vessel at step 4, while stirring to dissolve.
6. Add 8 g of item 8 (25°C) in a separate container and dissolve items 6 and 7 using stirrer and transfer to the drops manufacturing vessel at step 5.
7. Add item 4 to the drops manufacturing vessel at step 6 while mixing.
8. Add 5 g of item 8 (25°C) in a separate container and dissolve item 1 using stirrer.
9. Transfer this solution to the drops manufacturing vessel at step 7 while mixing.
10. Check and record the pH (limit 3.4 to 3.6).
11. Adjust the pH if required using 5% aqueous solution of citric acid or sodium citrate.
12. Make up the volume up to 1 L with item 8 (25°C).
13. Assemble the membrane filter of 0.2 micron. Filter the solution and collect the filtrate in clean high-density polyethylene (HDPE) containers.

Metoclopramide Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
30.00	1	Hydroxyethyl cellulose	6.00
4.00	2	Methyl paraben	0.80
1.00	3	Propyl paraben	0.20
5.00	4	Sorbic acid	1.00
14.25	5	Citric acid (monohydrate)	2.85
4.60	6	Sodium citrate	0.92
7.50	7	Saccharin sodium	1.50
5.00	8	Metoclopramide HCl (14% excess)	1.14
40.00	9	Alcohol (ethanol 95%)	8.00
25.00	10	Propylene glycol	5.00
6.50	11	Flavor	1.30
10.00	12	Caramel	2.00
0.50	13	Flavor	0.10
—	14	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 200.0 g of item 14 to the mixer and heat to 90˚C.
2. Sprinkle item 1 slowly while mixing at 20 rpm in manual mode. Check that item 1 is dispersed completely without forming lumps.
3. Start the homogenizer at high speed with recirculation, vacuum 0.4 bar.
4. Homogenize for 15 minutes at high speed. Cool to about 60˚C.
5. Add 200.0 g of item 14 in a storage container.
6. Transfer the homogenized mucilage to the storage container (step 5).
7. Add 500.0 g of item 14 to the syrup vessel and heat to 90˚C.
8. Add items 2, 3, and 4 to the syrup vessel and mix at high speed for 15 minutes to dissolve. Start cooling until temperature reaches at 50˚ to 60˚C.
9. Withdraw a portion of the solution and check that it is clear and colorless.
10. Transfer the mucilage to the syrup vessel and mix at high speed for 15 minutes. Start cooling and cool to 30˚C.
11. Add 20.0 g of item 4 (25˚C) in a separate container, dissolve items 5 and 6 by using stirrer, and add solution to the manufacturing vessel.
12. Add 10.0 g of item 14 (25˚C) in a separate container, dissolve item 7 by using stirrer, and add solution to the manufacturing vessel.
13. Withdraw a portion of the solution and check that it is clear and colorless.
14. Add 10.0 g of item 14 (25˚C) in a separate container, dissolve item 8 by using stirrer, and add solution to the manufacturing vessel.
15. Rinse the container with 5.0 g of item 14 (25˚C) cooled, and transfer the rinsing to the syrup vessel. Mix at high speed for 20 minutes.
16. Withdraw a portion of the solution and check that it is clear and colorless.
17. Mix items 10 and 9 in a clean stainless steel container. Add items 12, 11, and 13 and mix well manually.
18. Transfer the solution to the manufacturing vessel and mix for 15 minutes at high speed.
19. Make-up the volume to 1.0 L with item 14 (25˚C) and, finally, mix for 20 minutes at high speed.
20. Check and record the color and pH (limit 2.9 to 3.1). Color should be clear to faint yellow.
21. Suspend 1.0 g of the filter aid in 40.0 g of cooled item 14 (25˚C), and stir well, Allow the filter aid to settle, Decant off the water.
22. Transfer the washed filter aid to the syrup vessel while mixing. Mix for 30 minutes at high speed.
23. Assemble the filter press.
24. Wash the filters using about 250 L purified water (25˚C) by passing through filters at 0.2 bar.
25. Filter the syrup at 1.0 bar. Recirculate about 100 to 150 mL syrup.
26. Transfer the filtered syrup to the storage vessel.

Metronidazole Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
125.00	1	Metronidazole (use metronidazole benzoate)	40.20
7.50	2	Methyl paraben	1.50
1.00	3	Propyl paraben	0.20
2500.00	4	Sucrose	500.00
7.50	5	Saccharin sodium	1.50
8.75	6	Sodium phosphate monobasic	1.75
8.75	7	Sodium phosphate dibasic	1.75
40.00	8	Magnesium aluminium silicate	8.00
30.00	9	Microcrystalline cellulose	6.00
650.00	10	Propylene glycol	130.00
7.50	11	Lemon flavor	1.50
7.50	12	Bergamot flavor	1.50
—	13	Water, purified	q.s. to 1 L

Note. For 200 mg/5 mL strength use 64.400 g of metronidazole benzoate.

MANUFACTURING DIRECTIONS

1. Disperse item 1 in item 10 in a stainless steel vessel, using stirrer. Make smooth slurry and keep aside for use later.
2. Add 186.0 g of item 13 to a vessel and heat to 90˚ to 95˚C. Dissolve items 2 and 3 while mixing.
3. Add and dissolve item 4 while mixing at a temperature of 90˚ to 95˚C.
4. Cool down to 50˚ to 55˚C.
5. In a stainless steel container dissolve item 5 in 4.0 g of item 13 and add to the vessel while mixing.
6. Filter the syrup. Collect the syrup in stainless steel tank.
7. Disperse item 8 in 120.0 g of hot item 13 (70˚ to 75˚C) in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes. Transfer the dispersion into mixer by vacuum.
8. Mix and homogenize at temperature 70˚ to 80˚C, mixer speed 18 rpm, homogenizer at high speed and vacuum 0.4 to 0.6 bar for 10 minutes.
9. Cool down to 25˚ to 30˚C.
10. Disperse item 9 in 120.0 g of item 13 in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes to make smooth dispersion.
11. Transfer the filtered syrup from step 2.4 and transfer Avicel mucilage from step 4 to mixer. Set the mixer to 25˚ to 30˚C, 18 rpm; high speed and vacuum 0.4 to 0.6 bar.
12. Mix and homogenize for 10 minutes.
13. Dissolve items 6 and 7 in 12.0 g of item 13 and add to mixer while mixing.
14. Add metronidazole benzoate and propylene glycol dispersion (step 1) to mixer.
15. Rinse the drug container with 10.0 g of item 13 and add the rinsing to mixer to avoid loss.
16. Add items 11 and 12 to mixer. Make up the volume to 1.0 L with item 13.
17. Mix and homogenize for 20 minutes at high speed, vacuum 0.4 to 0.6 bar. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to stainless steel storage tank, previously sanitized by 70% ethanol.
18. Do not store the bulk suspension more than 48 hours in the storage tank without stirring. Before filling, stir not less than 30 minutes for uniform dispersion to avoid problem of content uniformity.

Minoxidil Solution

Minoxidil 5% w/v, alcohol, 30% v/v, propylene glycol, 50% v/v, and purified water.

Mint Oil Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
35.00	1	Peppermint oil	35.00
138.00	2	Cremophor RH 40	138.00
520.00	3	Ethanol 96%	520.00
307.00	4	Water	307.00

MANUFACTURING DIRECTIONS

1. Mix peppermint oil with Cremophor RH 40, and stir well.
2. Slowly add ethanol and water. A clear, colorless liquid of low viscosity is the result.

Mint–Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Mint oil	20.00
0.40	2	Menthol	0.40
0.90	3	Eucalyptus oil	0.90
10.00	4	Alpha-bisabolol (BASF)	10.00
0.60	5	Thymian oil	0.60
40.00	6	Cremophor RH 40	40.00
4.50	7	Saccharin sodium	4.50
2.0	8	Sodium citrate	2.0
5.0	9	Citric acid	5.0
0.20	10	Sodium fluoride	0.20
50.00	11	Glycerol	50.00
50.00	12	Lutrol F 127	50.00
0.60	13	Salicylic acid	0.60
1.00	14	Benzoic acid	1.00
175.00	15	Sorbitol, crystalline	175.00
216.00	16	Ethanol 96%	216.00
q.s.	17	Sicovit colorant	q.s.
q.s.	18	Water	48.4

MANUFACTURING DIRECTIONS

1. Mix components 1 to 6 and heat to about 60˚C.
2. Prepare solution of items 7 to 18, heat to about 60˚C.
3. Add this solution slowly to the well-stirred mixture of items 1 to 6. The result is a clear, colored liquid having a fresh mint taste.

Mometasone Furoate Nasal Spray

Nasonex nasal spray, 50 mcg is a metered-dose, manual-pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate, calculated on the anhydrous basis, in an aqueous medium containing glycerin, micro-crystalline cellulose and carboxymethylcellulose sodium, sodium citrate, 0.25% w/w phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80. The pH is between 4.3 and 4.9.

Monosulfiram Solution

Bill of Materials			
Scale (%, w/w)	**Item**	**Material Name**	**Quantity/kg (g)**
25.00	1	Monosulfiram	250.00
10.00	2	Dispersol	100.00
q.s.	3	Methylated spirit	q.s. to 1 kg

MANUFACTURING DIRECTIONS

1. Liquefy item 1 by warming to 40˚C.
2. Charge item 3 in a suitable dry, stainless steel mixing vessel.
3. Add item 2 to step 2 and then add item 1 with constant stirring until clear solution obtained.
4. Filter through a suitable clarifying filter.

Multivitamin and Calcium Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/100 (g)**
0.10	1	Vitamin A palmitate	10.0 mg
0.50 mcg	2	Vitamin D 40 million U/G	0.05 mg
1.00	3	Vitamin E acetate (BASF)	100.0 mg
0.020	4	Butylhydroxytoluene	2.0 mg
45.00	5	Cremophor RH 40	4.5
100.00	6	Water, purified	10.0
450.00	7	Saccharose	45.0
2.00	8	Methyl parabene	200.0 mg
0.80	9	Citric acid	80.0 mg
96.00	10	Glycerol	9.6
0.70	11	Calcium gluconate	70 mg
250.00	12	Water	25.0
0.150	13	Thiamine hydrochloride (BASF)	15.0 mg
0.150	14	Riboflavin 5'-phosphate sodium	15.0 mg
0.550	15	Nicotinamide	55.0 mg
0.150	16	Pyridoxine hydrochloride (BASF)	15.0 mg
3.00	17	Ascorbic acid, crystalline (BASF)	300.0 mg
1.00	18	Sorbic acid	100.0 mg
50	19	Propylene glycol	5.0

MANUFACTURING DIRECTIONS

1. Heat items 1 to 5 and item 6 separately to about 60°C and mix slowly with stirring to obtain a clear solution.
2. Dissolve items 7 to 9 in the hot solution of items 10 to 12 to obtain a clear solution.
3. Mix all the solutions on cooling, and add solutions of items 13 to 19.
4. Adjust the pH value to from 4.0 to 4.1.
5. Pass nitrogen through the solution for 10 minutes and fill in flasks under nitrogen.

Multivitamin Drops

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
8.00	1	Vitamin A palmitate 1.7 MM U/g (BASF)	8.00
0.130	2	Vitamin D3 40 MM U/g	0.130
5.00	3	Vitamin E acetate (BASF)	5.00
150.0	4	Cremophor EL (or Cremophor RH 40)	150.0
2.00	5	Parabens	2.00
525.00	6	Water	525.00
4.00	7	Thiamine hydrochloride (BASF)	4.00
2.00	8	Riboflavin 5-phosphate sodium	2.00
2.00	9	Pyridoxine hydrochloride (BASF)	2.00
2.00	10	Nicotinamide	2.00
0.20	11	Sodium bisulfite	0.20
200.00	12	Propylene glycol	200.00
q.s.	13	Water	10.0 g
q.s.	14	Hydrochloric acid	q.s.

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 to 4 to about 60˚C, and stir strongly.
2. Slowly add solution of items 5 and 6 at 60˚C.
3. To the obtained clear solution, add solution of items 7 to 13.
4. Adjust the pH, with item 14, to about 4.
5. Bring to volume.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/100 mL (g)**
0.170	1	Vitamin A palmitate 1.7 MM U/g (BASF)	17.0 mg
0.001	2	Vitamin D3 40 MM U/g	0.1 mg
0.010	3	Butylhydroxytoluene	1.0 mg
30.00	4	Cremophor RH 40	3.00
1.00	5	Parabenes	0.10
170.00	6	Water	17.00
0.50	7	Thiamine hydrochloride (BASF)	0.05
0.20	8	Riboflavin phosphate sodium	0.02
0.20	9	Pyridoxine hydrochloride (BASF)	0.02
2.50	10	Ascorbic acid, crystalline (BASF)	0.25
50.0	11	Water	5
q.s.	12	Sugar syrup	q.s. to 100 mL

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 to 4 to about 65˚C, and stir well.
2. Add very slowly item 6 to the warm solution (65˚C).
3. Mix with solution of items 7 to 11 and add item 12 to make up the volume. Parabens are generally a 1:10 ratio of methyl and propyl paraben.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/100 mL (g)**
170 U	1	Vitamin A palmitate 1.7 MMM U/g (BASF)	0.010
2.00 U	2	Vitamin D 40 MMM U/g	0.05 mg
1.00	3	Vitamin E acetate (BASF)	0.10
0.020	4	Butylhydroxytoluene	0.0020
45.0	5	Cremophor RH 40	4.50
100.00	6	Water	10.00
450.00	7	Saccharose	45.00
2.00	8	Methyl Parabene	0.20
0.080	9	Citric acid	0.080
9.60	10	Glycerol	9.60
250.00	11	Water	25.00
0.150	12	Thiamine hydrochloride (BASF)	0.015
0.150	13	Riboflavin 5'-phosphate sodium	0.015
0.55	14	Nicotinamide	0.055
0.150	15	Pyridoxine hydrochloride (BASF)	0.015
3.00	16	Ascorbic acid, crystalline (BASF)	0.30
1.00	17	Sorbic acid	0.10
5.0	18	Propylene glycol	5.00

MANUFACTURING DIRECTIONS

1. Heat items 1 to 5 and item 2 separately to about 60°C and mix slowly with stirring to obtain a clear solution.
2. Dissolve items 7 to 9 in the hot solution of items 10 and 11 to obtain a clear solution.
3. Mix the cool solutions and then add items 12 to 18 and adjust the pH value to 4.0 to 4.2.
4. Pass nitrogen for 10 min through the solution and fill under nitrogen cover. Provides 1 to 2 RDA/20 mL.

Multivitamin with Fluoride Infant Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/1000 L (g)**
8.00	1	Niacin, USE niacinamide, 5% excess	8.33
0.60	3	Riboflavin, USE riboflavin-5′-phosphate sodium, 2% excess	0.84
0.50g	5	Methy paraben	0.50
1.00	6	Acid benzoic	1.00
5000 U	7	Vitamin E, USE D-alpha tocopheryl polyethylene glycol 1000 succinate, 20% excess	13.82
400 U	9	Vitamin D, USE viosterol in corn oil (synthetic oleovitamin D, 25% excess)	0.52
1500 U (0.45 mg)	11	Vitamin A palmitate synthetic A palmitate 1 MM U/g	1.44
35.00	14	Acid, ascorbic white powder, 33% exc;	46.55
0.50	15	Thiamine hydrochloride, 44% excess	0.72
0.40	16	Pyridoxine, USE pyridoxine hydrochloride	0.48
0.25	18	Fluoride, USE sodium fluoride powder	0.55
4.01	20	Caramel acid proof	4.01
0.26	21	Oil Orange Terpeneless	0.25
0.00001 mL	22	Alcohol, ethanol, 190 proof	0.101 mL
q.s.	23	Water, purified, distilled	q.s.
q.s.	24	Acid hydrochloric	q.s.
q.s.	25	Sodium hydroxide	q.s.
q.s.	26	Carbon dioxide gas	q.s.

MANUFACTURING DIRECTIONS

Use only stainless steel tanks; minimize vortex formation to prevent aeration. Product attacks glass; avoid contact with glass.

1. Charge 350 mL of purified water into the stainless steel-jacketed main tank.
2. Start mixing. Add, in order, niacinamide, riboflavin, sodium fluoride, methylparaben, and benzoic acid.
3. Rinse the interior walls of tank with approximately 16 mL purified water.
4. Continue mixing for the balance of the process.
5. Heat the main tank to 95°C to dissolve ingredients. When the solution is complete, cool below 85°C (range 80° to 90°C).
6. Add vitamin E to another tank, if necessary, by heating vitamin E container. Melt vitamin E in the tank.
7. Add viosterol and vitamin A and heat to 60° to 65°C with mixing.
8. Start bubbling in CO_2. Mix slowly for 10 minutes or longer to produce a clear solution. Start CO_2 gas protection on the main mixing tank and continue for the balance of the process.
9. With the main batch at 85° to 90°C, add the solution of vitamins E, D, and A at 60° to 65°C, with mixing. The addition may cause the temperature of the main batch to drop below the specified range; readjust to 85° to 90°C.
10. Mix and maintain at this temperature until solution is complete, after which cool to below 30°C. Add the glycerin with mixing. Adjust the temperature to the 25° to 5°C range and maintain at this temperature before proceeding.
11. Add and dissolve with mixing in the following order: ascorbic acid, thiamine, pyridoxine, and caramel. Rinse the caramel container with approximately 3 mL of water, and add the rinsings.
12. Rinse the tank inner walls and mixer shaft with approximately 3 mL water.
13. Dissolve the orange oil with mixing in the alcohol and add to solution.
14. Continue mixing for at least 30 minutes to ensure a homogenous product.
15. Stop mixing, take pH (range 3.1 to 3.3). If necessary, adjust with 10% sodium hydroxide or 10% hydrochloric acid (prepared by adding 1 mL hydrochloric acid, reagent grade, with 3.3 mL purified water). Mix.

16. Stop mixing and allow to stand for at least 4 hours to eliminate entrapped CO_2 gas.
17. In a separate tank, properly cleaned, boil at least 65 mL of purified water for at least 15 minutes, cool while bubbling CO_2 into it, and hold at 30°C and adjust pH in the range 3.1 to 3.3.
18. Filter using a lint-free paper; do not use filter aids.
19. Recirculate product back to main mixing tank until clear. Flush a storage tank with CO_2 for at least 10 minutes with the CO_2 valve completely open.
20. Filter product into this storage tank. Fill under carbon dioxide cover.

Nafarelin Acetate Nasal Solution

Synarel nasal solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium hydroxide, or hydrochloric acid (to adjust pH), sorbitol, and purified water.

Nevirapine Suspension

Viramune oral suspension is for oral administration. Each 5 mL of Viramune suspension contains 50 mg nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methylparaben, propylparaben, sorbitol, sucrose, polysorbate 80, sodium hydroxide, and water.

Nicotine Spray

Each 10-mL spray bottle contains 100 mg nicotine (10 mg/mL) in an inactive vehicle containing disodium phosphate, sodium dihydrogen phosphate, citric acid, methylparaben, propylparaben, edetate disodium, sodium chloride, polysorbate 80, aroma, and water. The solution is isotonic with a pH of 7. It contains no chlorofluorocarbons.

Nimesulide Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Nimesulide	10.00
400.00	2	Sucrose	400.00
49.00	3	Propylene glycol	49.00
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	0.20
2.80	6	Sodium benzoate	2.80
0.20	7	Disodium edentate	0.20
0.50	8	Sodium citrate	0.50
0.10 mL	9	Sorbitol solution 70%	100 mL
4.00	10	Carboxymethyl cellulose sodium	4.00
2.00	11	Aerosil 200	2.00
3.30	12	Citric acid	3.30
1.00	13	Hydroxypropyl methyl cellulose	1.00
0.48	14	Simethicone emulsion	0.48
q.s.	15	Flavor	q.s.
q.s.	16	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. In a suitable stainless steel container heat item 16 to 70°C.
2. Add and dissolve sodium benzoate, disodium edentate, and sodium citrate.
3. Filter though a filter press.
4. Add sugar till completely dissolved.
5. Filter again through a filter press.
6. In a separate container charge propylene glycol and sorbitol solution. Add carboxymethyl cellulose and aerosol homogenizes and store for a few hours.
7. Add and mix in step 5 hydroxypropyl methyl cellulose and simethicone emulsion.
8. Add item 1 and make a slurry in step 6.
9. Add step 7 into step 4 and make up the volume with item 16.

Nimodipine Capsules

Each liquid-filled capsule contains 30 mg nimodipine in a vehicle of glycerin, peppermint oil, purified water, and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water, and titanium dioxide.

Nitroglycerin Lingual Spray

Nitrolingual Pumpspray (nitroglycerin lingual spray 400 mcg) is a metered-dose spray containing nitroglycerin. This product delivers nitroglycerin (400 mcg per spray, 75 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients are medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, and peppermint oil.

Norephedrine Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
40.00	1	DL-Norephedrine hydrochloride	40.00
10.00	2	Parabens	10.00
50.00	3	Saccharin sodium	50.00
30.00	4	Kollidon 90 F	30.00
500.00	5	Sorbitol solution	500.00
460.00	6	Water	460.00

MANUFACTURING DIRECTIONS

1. Dissolve the parabens in the hot water (90° to 95°C).
2. Add the sorbitol, cool to room temperature, and dissolve the other components.
3. To prevent of discoloration of Kollidon in the solution during storage, 0.1 to 0.5% of cysteine could be added as antioxidant.
4. Flavors should be added to adjust the required taste.

Nystatin Oral Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
21.05	1	Nystatin microfine (paticles size not less than 90% below 45 µm, 100% below 80 µm; based on potency of 5500 U/g anhydrous; adjust accordingly; 10% overage)	21.050
600.00	2	Sucrose	600.000
1.80	3	Methyl paraben	1.8000
0.20	4	Propyl paraben	0.2000
150.00	5	Sorbitol (70% solution)	150.000
5.00	6	Microcrystalline cellulose	5.000
10.00	7	Glycerin	10.000
2.00	8	Carboxymethylcellulose sodium	2.000
2.00	9	Polysorbate 80	2.000
50.00	10	Glycerin	50.000
2.50	11	Saccharin sodium	2.500
2.00	12	Flavor	2.000
30.00	13	Alcohol (ethanol 95%)	30.000
q.s.	14	Sodium hydroxide	0.174
q.s.	15	Hydrochloric acid (37%)	0.296
—	16	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 200.0 g of item 16 (90˚ to 95˚C) into mixer and heat to 90˚C to 95˚C. Dissolve items 3 and 4 while mixing. Add and dissolve item 2 while mixing at a speed of 18 rpm.
2. Cool down to about 50˚ to 55˚C.
3. Filter the syrup. Collect the syrup in clean stainless steel tank. Avoid any loss of syrup. Clean the mixer.
4. Transfer the sugar syrup from stainless steel tank into the mixer.
5. Add 100.0 g of item 5 into mixer while mixing.
6. Disperse item 6 in the mixture of 50.0 g of item 16 (25˚ to 30˚C) and 50.0 g of item 5 in a stainless steel drum while mixing with stirrer.
7. Disperse item 8 in item 7 in a stainless steel drum while mixing with stirrer. Add 30.0 g of item 16 (90˚C) to the solution. Stir until it becomes clear. Cool to 30˚C.
8. Transfer the dispersion from step 3 and 4 into mixer. Mix and homogenize under vacuum 0.4 to 0.6 bar for 10 minutes. Stop homogenizer and keep continuous mixing.
9. Dissolve item 9 in 50.0 g of item 16 (50˚C) in a stainless steel container while mixing by stirrer. Add item 10 into it. Disperse item 1 while stirring by stirrer. Cool to 30˚C. Add the drug dispersion into mixer while mixing.
10. Dissolve item 11 in 15.0 g of item 16 (25˚ to 30˚C) in a stainless steel container while stirring by stirrer. Add to mixer while mixing.
11. Add items 13 and 12 into mixer while mixing.
12. Homogenize high speed, and vacuum 0.4 to 0.6 bar. Mix and homogenize for 10 minutes.
13. Dissolve item 14 in 7.0 g of item 16 in a stainless steel container. Add slowly into the mixer while mixing.
14. Dissolve item 15 carefully in 7.0 g of item 16 in a stainless steel container. Slowly add the required quantity into mixer to adjust the pH between 6.8 and 7.1.
15. Make up the volume with item 16, up to 1 L. Mix for 5 minutes.

Nystatin Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
22.50	1	Nystatin	22.50
57.50	2	Kollidon CL-M	57.50
20.00	3	Kollidon 90F	20.00
248.00	4	Sorbitol	248.00
5.00	5	Citric acid	5.00
q.s.	6	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1, 2, and 4 in a suitable stainless steel vessel and suspend in item 6; mix well.
2. Add item 3 slowly while stirring and in small portions and then follow up with vigorous stirring to obtain smooth suspension. Homogenize if necessary.
3. Fill.

Naproxen Suspension

Naprosyn (naproxen) suspension for oral administration contains 125 mg/5 mL of naproxen in a vehicle containing sucrose, magnesium aluminum silicate, sorbitol solution, and sodium chloride (30 mg/5 mL, 1.5 mEq), methylparaben, fumaric acid, FD&C yellow no. 6, imitation pineapple flavor, imitation orange flavor, and purified water. The pH of the suspension ranges from 2.2 to 3.7.

Ofloxacin Otic Solution

Floxin otic contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
3.00	1	Ofloxacin	3.00
q.s.	2	Vehicle (pluraflo 1220 45.48%, ethanol 5.05%, propylene glycol 41.23%, anhydrous glycerin 8.24)	q.s. to 1 L
q.s.	3	Perfumes	q.s.

MANUFACTURING DIRECTIONS

1. Add propylene glycol, pluraflo, glycerine, and ethanol to a clean vessel.
2. While stirring, add ofloxacin. Stir until a clear solution is obtained.
3. Add perfume and mix until uniform.

Omeprazole Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Omeprazole free base	20.00
q.s.	2	Vehicle (pluronic F127 34.07%, ethanol 10.43%, propylene glycol 42.18%)	1 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00
2.50	5	Sodium saccharin	2.50
1.10	6	Monoammonium glycerhizzinate	1.10
3.50	7	Acesulfame	3.50
q.s.	8	Flavor	q.s.

MANUFACTURING DIRECTIONS

1. Add propylene glycol and poloxamer to a clean vessel (main mix).
2. While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer.
3. Once a uniform solution is obtained, remove from heat source and continue mixing.
4. In a separate vessel (alcohol premix) add alcohol, omeprazole base, and monoammonium glycerizzinate and mix until uniform. In another vessel (water premix), add water, EDTA, sodium saccharin, acesulfame, and sodium metabisulfite.
5. Mix until all materials are dissolved.
6. Add the alcohol containing premix to the main mixing vessel containing the poloxamer.
7. Mix until uniform.
8. While stirring, add the water containing premix to the main vessel and continue to mix until uniform.
9. Subsequently, add desired flavor component and mix until uniform.

Phenylpropanolamine Controlled-Release Capsule

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
33.00	1	Phenylpropanolamine	33.00
q.s.	2	Vehicle (pluraflo 1220 70.12%, ethanol 2.26%, anhydrous glycerin 16.35%)	q.s. to 1 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00

MANUFACTURING DIRECTIONS

1. Add alcohol, propylene glycol, EDTA, sodium metabisulfite, and phenylpropanolamine to a clean vessel and begin mixing.
2. Subsequently, add pluraflo and glycerine to the vessel.
3. Mix until uniform.
4. This liquid may be filled into hard gelatin capsules that are then banded to prevent leakage, or it may be used as the fill for a soft elastic gelatin capsule. One capsule is made to contain 0.75 mL of the liquid and, taken three times daily, provides controlled release of the phenylpropanolamine active. After swallowing, the gelatin shell dissolves in the gastrointestinal tract and the liquid fill immediately transforms into a slow-dissolving gel that provides controlled release of the phenylpropanolamine.

Ondansetron Hydrochloride Dihydrate Oral Solution

Each 5 mL of Zofran Oral Solution contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron. Zofran Oral Solution contains the inactive ingredients citric acid anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

Orciprenaline Sulfate and Clobutinol Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
10.00	1	Natrosol 250 M	2.00
5.00	2	Sodium benzoate	1.00
10.00	3	Saccharin sodium	2.00
35.00	4	Ammonium chloride	7.00
26.24	5	Citric acid	5.25
4.00	6	Sodium citrate	0.80
2500.00	7	Sorbitol 70%	500.00
500.00	8	Glycerin	100.00
5.00	9	Orciprenaline sulfate, 5% excess	1.05
20.00	10	Clobutinol hydrochloride	4.20
40.40	11	Alcohol	8.00
0.20	12	Anise oil	0.04
q.s.	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. In a suitable stainless steel mixing vessel, charge 250 mL of item 13 and heat to 70° to 75°C. Add item 1 and mix well; cool to room temperature.
2. In 10 mL of item 13 add and dissolve item 2 and 3 and add to step 2.
3. In 20 mL of item 13 add and dissolve item 4 and add to step above.
4. In a separate vessel add items 50 mL of item 13 and item 8 and mix well; add to step 4.
5. In 50 mL of item 13, add item 10, mix well, and add to step 5.
6. In 50 mL of item 13, add item 9, mix well, and add to step 6.
7. Adjust pH to 3.1 to 3.2 using item 5.
8. Filter through 100-micron filter and then through filter pads.
9. Make up volume and fill.

Oxitropium and Formeterol Nasal Spray

Charge 4.5 g of micronized oxitropium bromide and 0.675 g of micronized formoterol fumarate into a pressure-addition vessel. After sealing and evacuation thereof, 10.5 kg of HFA 227, which has previously been aerated with carbon dioxide and adjusted to a pressure of 6.25 bar (20°C) in another pressure addition vessel, is added. After homogenization of this mixture, the suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Oxycodone Hydrochloride Oral Concentrate Solution

Each 1 mL of Oxyfast concentrate solution contains oxycodone hydrochloride, 20 mg citric acid, FD&C yellow no. 10, sodium benzoate, sodium citrate, sodium saccharine, and water.

Oxymetazoline Hydrochloride Congestion Nasal Spray

Each milliliter of Afrin Severe Congestion Nasal Spray contains oxymetazoline hydrochloride 0.05%. It also contains benzalkonium chloride, benzyl alcohol, camphor, edetate disodium, eucalyptol, menthol, polysorbate 80, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Hydrochloride Nasal Solution

Bill of Materials			
Scale (g/100 mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.025	1	Oxymetazoline hydrochloride	0.25
0.03	2	Benzalkonium chloride (50% Solution)	0.30
0.05	3	Disodium edetate (sodium EDTA)	0.50
0.025	4	Sodium hydroxide (1N solution)	0.25
1.02	5	Monobasic sodium phosphate	10.20
2.80	6	Dibasic sodium phosphate	28.00
—	7	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

Oxymetazoline hydrochloride is toxic. There is a risk of serious intoxication if inhaled or swallowed. This product is a colorless, odorless membrane-filtered solution. Thus, make sure that the receiving tank for the filtered solution is cleaned and free of any contamination.

1. Heat 1.0 kg of item 7 up to 85° to 90°C in the manufacturing vessel. Hold the temperature at 85° to 90°C for 30 minutes.
2. Cool item 7 to 30°C and transfer into mobile tank.
3. Add 900.0 g of cold item 7 (from step 2) into manufacturing vessel.
4. Dissolve items 5, 6, 1, 2, 3, and 4 one by one while mixing in manufacturing vessel containing cold item 7.
5. After completion of addition mix for 20 more minutes.
6. Make up the volume to 1.0 L with cold item 7 and, finally, mix for 20 minutes.
7. Check and record the pH (limit 6.8 ± 0.1).
8. Filter the solution through Sartorius prefilter and membrane filter 0.2 μm into receiving tanks.

Oxymetazoline Moisturizing Nasal Spray

Each milliliter of Afrin Extra Moisturizing Nasal Spray contains oxymetazoline hydrochloride, 0.05%. It also contains benzalkonium chloride, edetate disodium, glycerin, polyethylene glycol, polyvinyl pyrrolidone, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Nasal Spray

Each milliliter of Afrin Original Nasal Spray and Pump Mist contains oxymetazoline hydrochloride, 0.05%. It also contains benzalkonium chloride, edetate disodium, polyethylene glycol, polyvinyl pyrrolidone, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Sinus Nasal Spray

Each milliliter of Afrin Sinus Nasal Spray contains oxymetazoline hydrochloride, 0.05%. It also contains benzalkonium chloride, benzyl alcohol, camphor, edetate disodium, eucalyptol, menthol, polysorbate 80, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Nasal Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (pluronic F127 40.27%, ethanol 26.18%, water 33.55%)	q.s. to 1 L
0.50	2	Oxymetazoline	0.50
1.50	3	Tyloxapol	1.50
0.40	4	Dibasic sodium phosphate	0.40
1.30	5	Monobasic potassium phosphate	1.30
0.40	6	Benzalkonium chloride	0.40
2.60	7	Chlorhexidine gluconate	2.60
0.10	8	Disodium EDTA	0.10

MANUFACTURING DIRECTIONS

1. Add the dibasic sodium phosphate, monobasic potassium phosphate, disodium EDTA, benzalkonium chloride, and oxymetazoline HCl to a clean vessel.
2. Add tyloxapol, chlorhexidine gluconate, and ethanol to the vessel.
3. Subsequently add the poloxamer and water to the vessel.
4. Mix until uniform.

Pheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
15.00	1	Pheniramine maleate	3.00
2980.00	2	Sugar	596.00
5.40	3	Methyl paraben	1.08
0.60	4	Propyl paraben	0.11
0.60	5	Citric acid monohydrate	0.11
1.50	6	Sodium citrate	0.30
3.50	7	Flavor	0.70
q.s.	8	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 700 mL item 8 in a suitable mixing vessel and heat to 90° to 95°C.
2. Add and mix item 2.
3. Add items 3 and 4 and mix to dissolve.
4. In separate vessels in about 100 mL item 8, add and dissolve items 5 to 7 and item 1 separately.
5. Add the two mixtures in step 3 to step 2 at room temperature.
6. Make up the volume.

Phenobarbital, Hyoscyamine Sulfate, Atropine Sulfate, and Scopolamine Hydrobromide Elixir

Each 5 mL (teaspoonful) of elixir (23% alcohol) contains phenobarbital 16.2 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, and scopolamine hydrobromide 0.0065 mg; D&C yellow no. 10, FD&C blue no. 1, FD&C yellow no. 6; flavors; glucose; saccharin sodium; water.

Phenylephrine Tannate and Chlorpheniramine Tannate Pediatric Suspension

Rynatan® pediatric suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the slate-purple-colored, natural strawberry–artificial currant–flavored suspension contains phenylephrine tannate 5 mg, chlorpheniramine tannate 4.5 mg, benzoic acid, FD&C blue no. 1, FD&C red no. 3, FD&C red no. 40, FD&C yellow no. 5, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, and sucrose.

Phenylephrine Tannate and Pyrilamine Tannate Suspension

RYNA-12 S suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the pink-colored, natural strawberry–artificial curran-flavored suspension contains phenylephrine tannate 5 mg, pyrilamine tannate 30 mg, benzoic acid, FD&C red no. 3, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, and sucrose.

Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
150.00	1	Polyethylene glycol 400	150.00
21.66	2	Acetaminophen	21.66
0.075 mL	3	Glycerin	75.000 mL
0.35 mL	4	Sorbitol solution	350.000 mL
1.00	6	Acid, benzoic	1.00
1.75	7	Saccharin sodium, powder, dihydrate	1.75
0.91	8	Phenylpropanolamine hydrochloride	0.92
0.065	9	Chlorpheniramine maleate (10% excess)	0.073
0.66	10	Dextromethorphan hydrobromide	0.67
20.00	11	Sodium CMC premium low viscosity	0.02
70.00	12	Dye	0.070
6.00	13	Dye	0.006
5.00	14	Ascorbic acid, USE sodium ascorbate fine powder	5.62
0.50	15	Flavor orange	0.50
0.25	16	Flavor orange	0.25
q.s.	17	Carbon dioxide gas	q.s.
q.s.	18	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. In a covered stainless steel container, heat 500 mL water to boiling. Boil for 30 minutes.
2. Turn off the heat and, while keeping the container covered, cool the water to 30˚C while purging it with carbon dioxide.
3. Keep this water in a covered container blanketed with carbon dioxide gas and use where indicated.
4. Transfer to the main stainless steel mixing tank the polyethylene glycol 400, cover, start bubbling CO_2 gas, and then, while mixing, slowly heat to 60˚ to 65˚C. Maintain at this temperature.
5. While mixing, add and dissolve the acetaminophen. Maintain the temperature and CO_2 protection.
6. When all the acetaminophen has dissolved, add, while mixing, the glycerine and sorbitol.
7. Continue mixing while maintaining the temperature and CO_2 gas protection until used later. Do not allow the temperature to go above 65˚C. During this mixing period, remove samples through the bottom valve of the mixing tank and inspect for clarity. Return samples to the mixing tank.
8. Continue mixing and sampling until absolutely clear.
9. In a separate stainless steel mixing tank, add 300 mL water, cover, and then heat to 90˚C.
10. While maintaining at this temperature, start bubbling CO_2 gas and then, while mixing, add and dissolve successively the benzoic acid, saccharin sodium, and phenylpropanolamine hydrobromide.
11. Continue mixing until all have dissolved. Reduce the temperature to 60˚ to 65˚C while mixing. Do not force cool.
12. To the solution in the main mixing tank add, while mixing and bubbling CO_2 gas, the solution from step above. Rinse the container with two lots of 5 mL carbon dioxide-saturated water and add the rinsings to the batch while mixing.
13. Continue mixing for 15 minutes while maintaining the temperature at 60˚ to 65˚C and CO_2 gas protection.
14. While mixing the batch, sprinkle on the sodium CMC.
15. Continue mixing until all the sodium CMC has been dispersed. Check to be sure there are no undissolved lumps.
16. Add CO_2-saturated water from step above and mix while cooling the batch to 30˚C. Dissolve the dyes in 10 mL carbon dioxide-saturated water then add to the batch with mixing.
17. Rinse the container with two lots of 5 mL the same water and add the rinsings to the batch. Mix until a homogenously colored batch is formed.
18. Stop bubbling in CO_2 gas but maintain CO_2 protection of the tank headspace. In a stainless

steel container, dissolve the sodium ascorbate in 25 mL carbon dioxide-saturated water, taking care to minimize exposure of the solution to air or light.

19. Mix all solutions, add rinsings where necessary, and continue mixing for 15 minutes.
20. Add the flavors, complete the batch to 1 L with carbon dioxide-saturated water and mix well for 1 hour.
21. Stop mixing, saturate the head space with CO_2, and leave overnight to release any entrapped air.

Phenytoin Suspension

Each teaspoonful of suspension contains 125 mg phenytoin, with a maximum alcohol content not greater than 0.6%. It also contains carboxymethylcellulose sodium; citric acid, anhydrous; flavors; glycerin; magnesium aluminum silicate; polysorbate 40; purified water; sodium benzoate; sucrose; vanillin; and FD&C yellow no. 6.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Phenytoin	50.00
80.00	2	Kollidon CL-M	80.00
10.00	3	Kollidon 90 F	10.00
q.s.	4	Preservative	q.s.
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge in a suitable stainless steel-jacketed vessel item 5 and heat to 90˚ to 95˚C.
2. Add and dissolve preservatives (e.g., parabens); stir to complete solution.
3. Cool to 40˚C.
4. Add item 3 and dissolve.
5. Add item 2 and suspend.
6. Add item 1 and suspend; homogenize if necessary.
7. Fill.

Pipenzolate Methyl Bromide and Phenobarbital Drops

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Pipenzolate methyl bromide	4.00
30.00	2	Phenobarbital	6.00
350.00	3	Alcohol	70.00
1000.00	4	Propylene glycol	200.00
450.00	5	Propylene glycol	90.00
33.00	6	Sodium saccharin	6.66
2500.00	7	Glycerin	500.00
5.00	8	Peppermint oil	1.00
1.65	9	Flavor	0.33
1.65	10	Flavor	0.33
0.20	11	Dye	0.04
10.00	12	Sodium citrate	2.00
17.70	13	Citric acid monohydrate	3.54
q.s.	14	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 150 mL item 14 in a suitable stainless steel vessel and heat to 90˚C for 1 hour and then cool to room temperature.
2. Add items 1, 6, 11, 12, and 13 and mix well.
3. In a separate vessel, charge items 4 and 7 and mix well for 10 minutes.
4. In a separate vessel, charge items 5, 2, 3, flavors, and item 7 and mix well.
5. Add step 4 to step 3 and mix well.
6. Add step 5 to step 1 and make up volume and mix well.
7. Fill.

Podofilox Solution

Condylox is the brand name of podofilox, an antimitotic drug that can be chemically synthesized or purified from the plant families Coniferae and Berberidaceae (e.g., species of Juniperus and Podophyllum). Condylox 0.5% solution is formulated for topical administration. Each milliliter of solution contains 5 mg of podofilox in a vehicle containing lactic acid and sodium lactate in alcohol 95%.

Polidocanol Wound Spray

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
5.00	1	I. Polidocanol	5.00
50.00	2	Kollidon VA 64	50.00
50.00	3	Ethocel® 20	50.00
20.00	4	Lutrol E 400	20.00
675.00	5	Ethyl acetate	675.00
200.00	6	Isopropanol	200.00

MANUFACTURING DIRECTIONS

1. Dissolve the items 1 to 4 in the solvent mixture of items 5 and 6.
2. Fill the solution into spray cans with the necessary quantity of propellant (e.g., propane/butane) or in a mechanical pump bottle.

Polyvinyl Pyrrolidone–Iodine Gargle Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (g)**
10.00	1	Polyvinyl pyrrolidone–iodine, powder, 35% excess	13.500
10.00	2	Glycerin (96%)	10.000
q.s.	3	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open unless necessary, as iodine may be liberated.

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add polyvinyl pyrrolidone–iodine powder, slowly to first step (with continuous stirring).
3. Stir for 30 minutes or until a clear brown solution is obtained.
4. Add glycerin to the manufacturing tank. Stir until uniform solution is obtained.
5. Make up volume to 1.0 L with purified water and mix well for 5 minutes.
6. Check pH (range: 2.0 to 4.0). Filter the solution through a 100-mesh nylon cloth and transfer to a stainless steel storage tank.
7. Keep the storage tank tightly closed.

Polyvinyl Pyrrolidone–Iodine Gargle Solution Concentrate

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (g)**
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
10.00	2	Propylene glycol Pharma	10.00
90.00	3	Ethanol 96%	90.00
800.00	4	Water	800.00

MANUFACTURING DIRECTIONS

1. Dissolve the polyvinyl pyrrolidone–iodine in the solvent mixture.
2. Brown transparent liquid: Dilute 10 mL the concentrate with about 100 mL water before use.

Polyvinyl Pyrrolidone–Iodine Liquid Spray

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
150.00	2	Kollidon VA 64	150.00
750.00	3	N-Propanol	750.00
750.00	4	Ethanol	750.00

MANUFACTURING DIRECTIONS

1. Dissolve Kollidon VA 64 in the mixture of solvents.
2. Slowly add polyvinyl pyrrolidone–iodine to the well-stirred solution.
3. Fill in aerosol cans with propellants such as propane and butane or with manual valves.

Polyvinyl Pyrrolidone–Iodine Mouthwash

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.0	1	Polyvinyl pyrrolidone–iodine	100.0
5.0	2	Sodium saccharin	5.0
2.0	3	Menthol	2.0
0.5	4	Oil aniseed	0.5
0.5	5	Eucalyptus oil	0.5
160.0	6	Polyethylene glycol 400	160.0
300.0	7	Ethanol	300.0
440.0	8	Water, purified	440.0

MANUFACTURING DIRECTIONS

1. Dissolve polyvinyl pyrrolidone–iodine powder and sodium saccharin in 440 g water to obtain a clear solution.
2. In a separate container add alcohol and mix and dissolve aniseed oil, eucalypus oil, menthol, and polyethylene glycol 400 to obtain a clear solution.
3. Add solution from step above and mix with stirring. Package in HDPE plastic bottles.

Polyvinyl Pyrrolidone–Iodine Mouthwash and Gargle Solution Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
75.00	1	Polyvinyl pyrrolidone–iodine 30/06	75.00
5.00	2	Saccharin sodium	5.00
150.00	3	Water	150.00
2.00	4	Menthol	2.00
1.00	5	Anise oil + eucalyptus oil, 1+1	1.00
150.00	6	Lutrol E 400	150.00
500.00	7	Ethanol 96%	500.00

MANUFACTURING DIRECTIONS

1. Dissolve polyvinyl pyrrolidone–iodine and saccharin in water and mix with solution of items 4 to 7.
2. A brown, transparent liquid having a fresh odor is formed.
3. Dilute 10 to 20 mL with a glass of water. A brown liquid is obtained having a fresh taste.

Polyvinyl Pyrrolidone–Iodine Scrub

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
75.00	1	Polyvinyl pyrrolidone–iodine, powder, 40% excess	105.000
250.00	2	Sodium lauryl sulfate	250.000
35.00	3	Lauric diethanolamide	35.000
q.s.	4	Water, purified, distilled	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add, by sprinkling, sodium lauryl sulfate in the manufacturing tank
3. Continue to mix slowly under vacuum and begin to heat until product temperature is 70°C.
4. Continue to mix vigorously under vacuum at 65° to 70°C for 15 minutes, or until completely dissolved. Do not add detergent quickly, as a gel may form that is difficult to dissolve. Stop mixer, release vacuum, and open tank.
5. Add and disperse the previously broken Lauric Diethanolamide in the warmed solution in step above.
6. Maintain vacuum and then mix vigorously for 30 minutes at 65° to 70°C or until completely dissolved.
7. Slowly cool under vacuum to room temperature with slow mixing. Do not force cool with cold water, otherwise the mixture will adhere to the walls of the manufacturing tank.
8. When temperature reaches 30°C, release vacuum and open tank.
9. While mixing slowly, add polyvinyl pyrrolidone–iodine in small portions.
10. Rinse the container of polyvinyl pyrrolidone–iodine with 150 mL purified water and add to the main tank. Do not keep the lid of the manufacturing or storage tank open unless necessary, as Iodine may liberate.
11. Mix under vacuum until a clear, reddish-brown solution is obtained.
12. Make volume to 1.0 L with purified water and mix well under vacuum for at least 15 minutes to ensure product uniformity and to deaerate the product.
13. Stop mixing, release the vacuum, and open the tank.
14. Check and record pH (range: 3.0 to 6.0).
15. Filter the solution through 100-mesh nylon cloth.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
0.230	2	Texapon K 12	0.230
1.40	3	Sodium biphosphate	1.40
0.30	4	Sodium citrate	0.30
20.80	5	Sodium hydroxyde solution, 1 molar	20.80
10.00	6	Glycerol	10.00
864.20	7	Water	864.20

MANUFACTURING DIRECTIONS

1. Dissolve Texapon K 12 in solution of items 3 to 7.
2. Slowly add polyvinyl pyrrolidone–iodine to the well-stirred solution. This creates a brown, transparent liquid having a pH of 4.5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
10.00	2	Natrosol® HR 250	10.00
2.00	3	Lutrol F 127	2.00
32.00	4	Sodium hydroxide, 1 molar solution	32.00
856.00	5	Water	856.00

MANUFACTURING DIRECTIONS

1. Dissolve Lutrol F 127 and then Natrosol in the water.
2. As soon as both are dissolved, slowly add the polyvinyl pyrrolidone–iodine to the well-stirred solution.
3. Adjust the pH with the sodium hydroxide solution to about 3.5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/Kg (g)
20.00	1	Tylose M 300	20.00
2.00	2	Texapon K 12	2.00
595.00	3	Citric acid solution 0.1 molar	595.00
283.00	4	Sodium biphosphate solution 0.2 molar	283.00

MANUFACTURING DIRECTIONS

1. Dissolve Tylose M 300 in the mixture of the citric acid and sodium biphosphate solutions.
2. Add Texapon and slowly dissolve the polyvinyl pyrrolidone–iodine. This creates a brown, clear solution having a certain viscosity and a pH of 3 to 4.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
3.00	2	Lutrol F 127	3.00
5.00	3	Lutrol E 400	5.00
432.00	4	Citric acid 0.1 molar solution	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$ 0.2 molar solution	460.00

MANUFACTURING DIRECTIONS

1. Dissolve the polyvinyl pyrrolidone–iodine (and Lutrol F 127) in the mixture of the buffer solutions (and Lutrol E 400).
2. A brown, clear solution is formed that has a low viscosity and a pH of about 4.5.
3. Items 2 and 3 can be deleted and compensated with item 5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/1000 Tabs. (g)**
100.00	1	Polyvinyl pyrrolidone–iodine powder, 35% excess	135.00
9.318	2	Acid, citric, anhydrous, powder	9.318
14.62	3	Sodium phosphate, dibasic, anhydrous	14.62
q.s.	4	Water, purified, distilled	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank. With gentle stirring, add citric acid into the purified water in the manufacturing tank.
2. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
3. Return samples to the manufacturing tank.
4. Continue mixing and sampling until the solution is completely clear.
5. With gentle stirring, add sodium phosphate, dibasic, into the solution. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity. Return samples to the manufacturing tank.
6. Continue mixing and sampling until the solution is completely clear. Make up volume to 1 L with purified water and mix well for 5 minutes.
7. Check and record pH (range: 4.8 to 5.2). Filter the solution through a 100-mesh nylon cloth.
8. Transfer into a suitable stainless steel storage tank and keep tightly closed. This solution should be freshly prepared and should not be stored for more than 24 hours.
9. Dissolve polyvinyl pyrrolidone–iodine in about 600 mL citric acid-phosphate buffer (pH 5.0) solution (made above) in a suitable stainless steel mixing tank.
10. Stir evenly for 10 minutes or until a clear, brown solution is obtained. Make up volume to 1 L with citric acid–phosphate buffer solution.
11. Mix well for 10 minutes.
12. Check and record pH (range: 3.0 to 4.5).
13. Filter the solution through a 100-mesh nylon cloth.
14. Transfer into a suitable stainless steel storage tank and keep tightly closed.

Polyvinyl Pyrrolidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
75.00	1	Polyvinyl pyrrolidone–iodine 30/06	75.00
250.00	3	Lutensit AES	250.00
40.00	4	Monoamide 150 MAW	40.00
q.s.	6	Floral bouquet	q.s.
635.00	7	Water	635.00

MANUFACTURING DIRECTIONS

1. Dissolve monoamide in hot water, cool to room temperature.
2. Dissolve polyvinyl pyrrolidone–iodine.
3. Add Lutensit to form a brown, clear, viscous solution.

Polyvinyl Pyrrolidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
75.00	1	Polyvinyl pyrrolidone–iodine 30/06	75.00
250.00	2	Neutronyx S 60	250.00
40.00	3	Super amide L 9	40.00
q.s.	4	Floral bouquet	q.s.
635.00	5	Water	635.00

MANUFACTURING DIRECTIONS

1. Dissolve super amide in hot water and then cool.
2. Dissolve polyvinyl pyrrolidone Iodine and add Neutronyx.
3. A brown, clear, viscous solution is formed, with pH of about 3.4.

Polyvinyl Pyrrolidone–Iodine Vaginal Douche Concentrate

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
5.00	2	Lutrol E 400	5.00
3.00	3	Lutrol F 127	3.00
432.00	4	Citric acid, 0.1 molar solution	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$, 0.2 molar solution	460.00

MANUFACTURING DIRECTIONS

1. Dissolve polyvinyl pyrrolidone–iodine and Lutrol F 127 in the mixture of the buffer solutions with Lutrol E 400.
2. A brown, clear solution is created having a low viscosity and a pH of about 4.3.

Polyvinyl Pyrrolidone–Iodine Viscous Solution

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
10.00	1	Polyvinyl pyrrolidone–iodine 30/06	10.00
15.00	2	Natrosol HR 250	15.00
q.s.	3	Buffer	q.s
q.s.	4	Water	975.00

MANUFACTURING DIRECTIONS

1. Dissolve polyvinyl pyrrolidone–iodine and natrosol in the well-stirred water.
2. Clear brown viscous liquid viscosity (Brookfield) of 7500 mPas is obtained.

Prednisone Oral Solution

Each 5 mL oral solution contains prednisolone 5 mg and alcohol 5% or 30%. Inactive ingredients include alcohol, citric acid, disodium edetate, fructose, hydrochloric acid, maltol, peppermint oil, polysorbate 80, propylene glycol, saccharin sodium, sodium benzoate, vanilla flavor, and water. Prednisone 30% alcohol solution contains citric acid, poloxamer 188, propylene glycol, and water.

Prednisolone Sodium Phosphate Oral Solution

PEDIAPRED (prednisolone sodium phosphate) oral solution is a dye-free, colorless to light-straw-colored, raspberry-flavored solution. Each 5 mL (teaspoonful) of PEDIAPRED contains 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) in a palatable, aqueous vehicle.

Prednisolone Syrup

The syrup contains 15 mg or 5 mg prednisolone in each 5 mL. Benzoic acid 0.1% is added as a preservative. The syrup also contains alcohol 5%, citric acid, edetate disodium, glycerine, propylene glycol, purified water, sodium saccharin, sucrose, artificial wild cherry flavor, and FD&C blue no. 1 and red no. 40.

Progesterone Capsules

Progesterone capsules contain micronized progesterone for oral administration. Capsules are available in multiple strengths to afford dosage flexibility for optimum management. Capsules contain 100 or 200 mg micronized progesterone. The inactive ingredients for 100 mg capsules include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow no. 10, and FD&C red no. 40. The inactive ingredients for capsules 200 mg include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow no. 10, and FD&C yellow no. 6.

Promethazine Hydrochloride Syrup

Each teaspoon (5 mL) of phenergan syrup plain contains 6.25 mg promethazine hydrochloride in a flavored syrup base with a pH between 4.7 and 5.2; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C red no. 33, D&C yellow no. 10, FD&C blue no. 1, FD&C yellow no. 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Each teaspoon (5 mL) of Phenergan Syrup Fortis contains 25 mg promethazine hydrochloride in a flavored syrup base with a pH between 5.0 and 5.5; alcohol, 1.5%. The inactive ingredients present are artificial and natural flavors, citric acid, saccharin sodium, sodium benzoate, sodium propionate, water, and other ingredients.

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Promethazine HCl (5% exces)	1.05
675.00	2	Sucrose	675.00
1.00	3	Citric acid (monohydrate)	1.00
2.40	4	Sodium citrate	2.40
0.50	5	Ascorbic acid	0.50
0.25	6	Sodium metabisulphite (sodium disulfite)	0.25
0.250	7	Sodium sulphite anhydrous	0.25
50.00	8	Alcohol (ethanol 95%)	50.00
0.15	9	Flavor	0.15
0.30	10	Flavor	0.30
0.50	11	Polysorbate 80	0.50
0.15	12	Caramel color	0.15
q.s.	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 400.0 g of item 13 to the manufacturing vessel and heat to 90° to 95°C.
2. Add item 2 while mixing at slow speed. After addition of item 2, mix for 30 minutes at high speed, temperature 90° to 95°C.
3. Cool down to 30° to 35°C while mixing at low speed.
4. Add items 3 and 4 to the manufacturing vessel while mixing and mix until dissolved.
5. Add items 6 and 7 to the manufacturing vessel while mixing and mix until dissolved.
6. Add item 5 to the manufacturing vessel while mixing and mix until dissolved.
7. Mix items 9 and 10 with item 8 and item 11 in a separate container by using a stirrer.
8. Mix for 10 minutes and add to the manufacturing vessel while mixing. Add 8.0 g of cold item 13 (25° to 30°C) in a separate container and dissolve item 12 by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing. Start flushing the syrup with nitrogen gas pressure at 20 to 40 psi.
10. Add 10.0 g of cold item 13 (cooled and nitrogen gas flushed) in a separate container with lid. Pass nitrogen gas at 20 to 40 psi pressure for 15 minutes.
11. Dissolve item 1 in nitrogen-flushed cold item 13 (25° to 30°C) by using stirrer.
12. Mix for 10 minutes and add to the manufacturing vessel while mixing.
13. Do not produce vortex. Make up the volume to 1 L with nitrogen-flushed item 13.
14. Continue flushing nitrogen gas at 20 to 40 psi pressure for 30 minutes while mixing at slow speed.
15. Check and record the pH (limit 4.5 to 5.5). If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
16. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.
17. Transfer the filtered syrup to the storage vessel. Flush with nitrogen gas and seal the tank.

Promethazine and Codeine Syrup

Each teaspoon (5 mL) of Phenergan VC with codeine contains 10 mg codeine phosphate (warning — this may be habit forming), 6.25 mg promethazine hydrochloride, and 5 mg phenylephrine hydrochloride in a flavored syrup base with a pH between 4.8 to 5.4; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C red no. 33, FD&C yellow no. 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Promethazine and Dextromethorphan Syrup

Each teaspoon (5 mL) of Phenergan with dextromethorphan contains 6.25 mg promethazine hydrochloride and 15 mg dextromethorphan hydrobromide in a flavored syrup base with a pH between 4.7 and 5.2; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C yellow 10, FD&C yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Promethazine Rectal Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Pluronic L62	q.s. to 1 L
2.50	2	Promethazine hydrochloride	2.50

MANUFACTURING DIRECTIONS

1. Mill and screen the promethazine HCl to reduce particle size.
2. Add the poloxamer and the promethazine HCl into a clean vessel.
3. Mix until uniform.

Promethazine Rectal Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Pluronic L62	q.s. to 1 L
10.00	2	Carbopol 974	10.00
2.50	3	Promethazine hydrochloride	2.50

MANUFACTURING DIRECTIONS

1. Mill the promethazine HCl to reduce particle size.
2. Sieve the carbomer and promethazine HCl and add to a clean vessel.
3. Add the poloxamer. Mix until uniform.

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
500.00	1	Sucrose	500.000
300.00	2	Glucose, liquid	300.000
150.00	3	Glycerine (96%)	150.000
30.00	4	D-Pseudoephedrine hydrochloride	30.000
1.00	5	Carbinoxamine maleate	1.000
4.00	6	Saccharin sodium powder	4.000
2.50	7	Sodium benzoate powder	2.500
1.25	8	Flavor	1.250
0.032	9	Dye	0.032
0.036	10	Dye	0.036
—	11	Acid hydrochloric reagent-grade bottles	q.s
1.320	12	Filter aid hyflo	1.320
455.00	13	Water, purified	455
q.s.	14	Sodium hydroxide for pH adjustment	q.s.

MANUFACTURING DIRECTIONS

1. Charge 315 mL purified water into a suitable tank. Begin heating water to 60˚ to 70˚C while adding sugar with stirring.
2. Stir until sugar is dissolved. Remove heat. Add glucose liquid and 125 g glycerine in this step.
3. Add and dissolve D-Pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing. Cool solution to 30˚ to 35˚C.
4. Mix flavor with 25 g of glycerin. Temperature of syrup must not be higher than 35˚C.
5. Dissolve dyes, if used, in 5 mL purified water and add to syrup with mixing. Adjust to pH 4.25 (range: 4.0 to 4.5), if necessary, with hydrochloric acid or sodium hydroxide.
6. q.s. to 1 L with purified water and mix well. Allow product to stand overnight to let entrapped air escape.
7. Readjust volume to 1 L with purified water.
8. Add and mix 1.320 g of filter aid hyflo to the product.
9. Circulate through a press. Filter into tank for filling.

Pseudoephedrine and Carbinoxamine Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
500.00	1	Sucrose	500.00
300.00	2	Glucose liquid	300.00
150.00	3	Glycerine	150.00
30.00	4	Pseudoephedrine hydrochloride	30.00
1.00	5	Carbinoxamine maleate	1.00
4.00	6	Saccharine sodium	4.00
2.50	7	Sodium benzoate	2.50
1.25	8	Flavor black currant	1.25
0.032	9	Dye red	0.032
0.036	10	Dye yellow	0.036
q.s.	11	Hydrochloric acid, to adjust pH	q.s.
1.32	12	Filter aid hyflow	1.32
q.s.	13	Water, purified	q.s. to 1 L
q.s.	14	Sodium hydroxide, to adjust pH	q.s.

MANUFACTURING DIRECTIONS

1. Charge 315 mL purified water into a suitable tank.
2. Begin heating water to 60˚ to 70˚C while adding sugar with stirring. Stir until sugar is dissolved.
3. Remove heat. Add glucose liquid and 40 g sorbitol solution with mixing. Hold balance of sorbitol for step 6.
4. Add and dissolve D-Pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing.
5. Cool solution to 30˚ to 35˚C.
6. Mix flavors with balance of sorbitol and add to syrup.
7. Add glycerine. Temperature of syrup must not be higher than 35˚C.
8. Dissolve dyes, if used, in 5 mL purified water and add to syrup with mixing. Adjust to pH 4.25 (range: 4.0 to 4.5), if necessary, with hydrochloric acid or sodium hydroxide.
9. q.s. to 1 L with purified water and and mix well.
10. Allow product to stand overnight to let entrapped air escape. Readjust volume to 1 L.
11. Add and mix 1.32 g of filter aid hyflo to the product. Circulate through a press until sparkling clear.
12. Filter into tank for filling. Fill into suitable approved containers.

Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
6.00	1	Pseudoephedrine HCl, 3.0% excess	6.18
600.00	2	Sucrose	600.00
100.00	3	Glycerin (glycerol)	100.00
100.00	4	Sorbitol (70% solution)	100.00
15.00	5	Propylene glycol	15.00
1.00	6	Methyl paraben	1.00
0.30	7	Propyl paraben	0.30
0.50	8	Saccharin sodium	0.50
0.02	9	Dye (if needed)	0.02
0.05	10	Menthol	0.05
0.132	11	Citric acid	0.13
1.150	12	Sodium citrate	1.15
—	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 390.0 g of item 13 to the manufacturing vessel and heat to 90˚ to 95˚C.
2. Add items 6 and 7 while mixing to dissolve at high speed.
3. Add item 2 while mixing at slow speed. Temperature 90˚ to 95˚C.
4. Mix for 1 hour at high speed. Cool down to 50˚C while mixing at slow speed.
5. Dissolve items 8 and 12 in 10.0 g of item 13 and add to the manufacturing vessel while mixing at high speed.
6. Dissolve item 11 in 10.0 g of item 13 and add to the manufacturing vessel while mixing at high speed. Load items 4 and 3 into the manufacturing vessel using transfer pump while mixing at high speed.
7. Mix for 5 minutes. Cool down to 30˚C while mixing at slow speed.
8. Add 20.0 g of item 13 (30˚C) in a separate container and dissolve item 1 by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed. Add 6.0 g of item 13 in a separate container and dissolve item 9 manually.
10. Add color to the manufacturing vessel while mixing at high speed.
11. Dissolve item 10 in item 5. Add this flavor mixture to the manufacturing vessel while mixing at high speed. Make up the volume to 1 L with item 13 and finally mix for 15 to 20 minutes at high speed.
12. Check and record the pH (limit 5.5 to 6.5 at 25˚C).
13. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 100 to 150 mL syrup.

Ribavirin Inhalation Solution

Virazole is a brand name for ribavirin, a synthetic nucleoside with antiviral activity. VIRAZOLE for inhalation solution is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100-mL glass vial contains 6 g ribavirin, and when reconstituted to the recommended volume of 300 mL with sterile water for injection or sterile water for inhalation (no preservatives added), contains 20 mg of ribavirin per milliliter, with a pH of approximately 5.5. Aerosolization is to be carried out in a small particle aerosol generator (SPAG-2) nebulizer only.

Risperidone Oral Solution

Risperdal is available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

Ritonavir Capsules

Norvir soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.

Ritonavir Oral Solution

Norvir oral solution is available for oral administration as 80 mg/mL ritonavir in a peppermint- and caramel-flavored vehicle. Each 8-ounce bottle contains 19.2 g ritonavir. Norvir oral solution also contains ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C yellow no. 6.

Ritonavir and lopinavir Oral Solution

Kaletra oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural and artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, polyvinyl pyrrolidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

Rivastigmine Tartarate Oral Solution

Exelon oral solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/mL rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow no. 10, purified water, sodium benzoate, and sodium citrate.

Salbutamol Aerosol

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/1000 units (g)**
1.17	1	Salbutamol, 10% excess	26.40
0.11	2	Oleic acid, 10% excess	2.64
277.61	3	Trichloromonofluoromethane	5664.00
721.09	4	Dichlorodifluoromethane	14,700.00

MANUFACTURING DIRECTIONS

1. Filter approximately 5 kg of the trichloromonofluoromethane and the oleic acid through a suitable 0.2-micron filter into a stainless steel concentrate container.
2. Slowly add the salbutamol to the solution in step 1 and mix for about 15 minutes.
3. Filter most of the remaining trichloromonofluoromethane through a suitable 0.2-micron filter into the suspension holding tank.
4. Add the slurry from step 2 to the holding tank.
5. Rinse the concentrate container with filtered trichloromonofluoromethane and add the rinses to the holding tank.
6. Make up the final mass of 5.693 kg with filtered trichloromonofluoromethane.
7. Mix for 5 minutes. Sample (to determine nonvolatile matter, range 0.49 to 0.53 w/w).
8. Fill 5.7 g of suspension into a clean aluminum vial and immediately crimp on the metering valve. Pressure fill, through metering valve, sufficient dichloro-difluorimethane to produce a final fill weight of 20.4 g. Check-weigh each aerosol to ensure that the fill weight is in the range of 20 to 20.8 g. At the start of manufacture, fill the vials and apply nonmetering valves. Pressure-test these vials using a special gauge adaptor to ensure the correct propellant mix is being used. The internal pressure measured at 22°C should be 50 to 60 psi.
9. Store the filled aerosols for a period of 2 weeks and check the weight again.
10. Test each aerosol by actuation to ensure correct operation.

Salbutamol Syrup Sugar Free

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.75	1	Citric acid (monohydrate)	4.15
10.00	2	Sodium benzoate	2.00
6.25	3	Sodium citrate	1.25
3.75	4	Saccharin sodium	0.75
2.00	5	Salbutamol sulfate, 20% excess	0.48
5.00	6	Sodium chloride	1.00
5.00	7	Strawberry flavor	1.00
10.00	8	Tangerine flavor	2.00
15.00	9	Hydroxypropyl methylcellulose (Methocel E4M)	3.00
—	10	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 700.0 g of item 10 to the manufacturing vessel and heat to 70˚C.
2. Add item 9 slowly while mixing at low speed. Mix for 30 minutes.
3. Cool down to 25˚C with continuous mixing at low speed.
4. Add 20.0 g of item 10 (25˚C) in a separate stainless steel container and dissolve items 6, 4, and 3 and add to the manufacturing vessel.
5. Add 20.0 g of item 10 (25˚C) in a separate container and dissolve item 1 by and add to the manufacturing vessel.
6. Add 20.0 g of item 10 (25˚C) in a separate container and dissolve item 2 and add to the manufacturing vessel.
7. Add 20.0 g of item 10 (25˚C) in a separate container and dissolve item 5 by and add to the manufacturing vessel.
8. Add items 7 and 8 to the manufacturing vessel while mixing.
9. Makeup the volume up to 1 L with item 10 (25˚C) and finally mix for 20 minutes at high speed.
10. Assemble the Seitz filter press and wash the filters using about 250 L purified water (25˚C) by passing through filters at 0.2 bar.
11. Filter the syrup at 1.5 bar. Recirculate about 30 to 40 mL syrup.
12. Transfer the filtered syrup to the storage vessel.

Salbutamol Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.00	1	Salbutamol sulphate (20%)	0.480
2500.00	2	Sucrose	500.000
5.00	3	Methyl paraben	1.000
1.00	4	Propyl paraben	0.20
5.00	5	Citric acid (monohydrate)	1.00
2.80	6	Sodium citrate	0.57
1000.00	7	Sorbitol (70% solution)	200.00
1.10	8	Flavor	0.22
1.10	9	Flavor	0.22
50.00	10	Propylene glycol	10.00
—	11	Water, purified,	q.s. to 1 L

MANUFACTURING DIRECTIONS

See above.

Salicylic Acid Collodion

Salicylic acid 17% w/w, alcohol, 26.3% w/w, t-Butyl alcohol, denatonium benzoate, flexible collodion, and propylene glycol dipelargonate.

Salmeterol Xinafoate Inhalation Aerosol

Salmeterol xinafoate inhalation aerosol contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It is a pressurized, metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of salmeterol xinafoate in a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with lecithin. 36.25 mcg of salmeterol xinafoate is equivalent to 25 mcg of salmeterol base. Each actuation delivers 25 mcg of salmeterol base (as salmeterol xinafoate) from the valve and 21 mcg of salmeterol base (as salmeterol xinafoate) from the actuator. Each 6.5-g canister provides 60 inhalations, and each 13-g canister provides 120 inhalations.

Bill of Materials			
Scale (mg/application)	**Item**	**Material Name**	**Quantity/1000 application (g)**
0.25	1	Salmeterol (used as salmeterol xinafoate)	0.250
7.28	2	Miglyol 829 (caprylic/capric diglycerol succinate)	7.280
0.15	3	Peppermint oil	0.150
0.18	4	Menthol	0.180
113.00	5	N-Butane	q.s. to 113.000

MANUFACTURING DIRECTIONS

1. Transfer Miglyol 829 by pumping from the released and tared container into mixing vessel.
2. After pumping Miglyol 829, set the propeller with optimum circulation and revolution to ensure no air entrapment.
3. Weigh out required amount of salmeterol xinafoate transfer directly into mixing vessel while mixing slowly.
4. Keep the preparation under stirring without interruption or change in rpm.
5. Dissolve menthol in peppermint oil at 25°C by slow stirring in another mixing vessel. Continue stirring until the solution becomes clear.
6. Transfer the clean menthol solution (step 5) into step 4 while stirring at the set speed. Continue stirring for 1 hour.
7. Store the base solution in aluminum can with polyethylene stopper and screw cap.

Scopolamine Nasal Spray

Charge 2.6 g of scopolamine into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved. After sealing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 8 bar (20) in another pressure-addition vessel is added by stirring. The solution obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Sertraline Hydrochloride Oral Concentrate

Sertraline hydrochloride is a selective serotonin reuptake inhibitor for oral administration. It is chemically unrelated to other selective serotonin reuptake inhibitors or tricyclic, tetracyclic, or other available antidepressant agents. It is supplied in a multidose 60-mL bottle. Each milliliter of solution contains sertralinehydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene. The oral concentrate must be diluted before administration.

Sertraline Hydrochloride Solution

ZOLOFT oral concentrate is available in a multidose 60-mL bottle. Each milliliter of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene.

Simethicone Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
144.00	1	Simethicone emulsion 30% (Simethicone Antifoam M30)[a]	144.00
60.00	2	Polyethylene glycol (PEG 6000)	60.00
1.50	3	Xanthan gum (Keltrol F)	1.50
1.50	4	Methylcellulose 4000 (Methocel A4M)	1.50
1.50	5	Potassium sorbate	1.50
1.20	6	Methyl paraben	1.20
0.20	7	Propyl paraben	0.20
1.500	8	Saccharin sodium	1.50
0.80	9	Banana green flavor	0.80
1.02	10	Citric acid (monohydrate)	1.02
0.24	11	Sodium citrate powder	0.24
—	12	Water, purified	q.s. to 1 L

[a]Equivalent to 43.2 mg of Simethicone

MANUFACTURING DIRECTIONS

1. Load 240 g of item 12 in mixer. Heat to 90° to 95°C. Dissolve items 6 and 7 by mixing with recirculation for 5 minutes.
2. Load item 2 in mixer. Mix to clear solution at 90° to 95°C for 5 minutes, under vacuum 0.4 to 0.6 bar.
3. Cool down to 25° to 30°C. Take the PEG-paraben solution out of the mixer and keep in a stainless steel container.
4. Load 512 g of item 12 in mixer. Heat to 90° to 95°C and then cool to 65° to 70°C.
5. Take out 208 g of item 12 (65° to 70°C) from the mixer in a stainless steel container. Disperse item 3 by continuous stirring by mixer.
6. Disperse item 4 in mixer containing item 12 at 65° to 70°C (step 4) while mixing and homogenizing at high speed for 5 minutes under vacuum 0.4 to 0.6 bar.
7. Cool to 20° to 25°C with continuous mixing and recirculation.
8. Add PEG-paraben solution from step 3 to mixer while mixing at speed 18 rpm.
9. Add item 3 mucilage from step 5 to mixer while mixing at speed 18 rpm.
10. Homogenize at high speed under vacuum 0.4 to 0.6 bar for 5 minutes while mixing.
11. Dissolve items 5 and 8 in 12 g of item 12 in a stainless steel container and add to mixer while mixing.
12. Add item 1 to the mixer while mixing.
13. Rinse the container of item 1 (step 12) with 12 g of item 12 and add the rinsing to the mixer.
14. Add item 9 to the mixer while mixing.
15. Mix and homogenize at low speed under vacuum 0.4 to 0.6 bar for 5 minutes.
16. pH is a critical factor for Simethicone emulsion. Limit is between 4.4 and 4.6 — carefully adjust the pH.
17. Add item 12 (25° to 30°C) to make up the volume up to 1 L.
18. Mix at slow speed under vacuum 0.4 to 0.6 bar for 5 minutes.
19. Filter the bulk through 630-micron sieve in a clean stainless steel storage tank.

Sirolimus Solution

Sirolimus is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. It is available for administration as an oral solution containing 1 mg/mL sirolimus; the inactive ingredients include phosphatidylcholine, propylene glycol, mono- and diglycerides, ethanol, soy fatty acids, and ascorbyl palmitate, and polysorbate 80. The oral solution contains 1.5 to 2.5% ethanol.

Sodium Chloride Nasal Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
90.00	1	Sodium chloride	90.00
3.00	2	Benzalkonium chloride solution 5%	3.00
q.s.	3	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 50% item 1 in a suitable stainless steel container and heat to 85° to 90°C.
2. Add and dissolve item 2 at room temperature.
3. Add item 1 and make up volume.

Stavudine for Oral Suspension

Zerit (stavudine) for oral solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL a 1 mg/mL stavudine solution on constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

Sucralafate Suspension

Carafate suspension for oral administration contains 1 g sucralfate per 10 mL. Carafate suspension also contains colloidal silicon dioxide, FD&C red no. 40, flavor, glycerin, methylcellulose, methylparaben, microcrystalline cellulose, purified water, simethicone, and sorbitol solution.

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
1000.00	1	Sucralafate	200.00
5.00	2	Methyl paraben	1.00
1.50	3	Propoyl paraben	0.30
1500.00	4	Sorbitol 70%	300.00
2.50	5	Saccharin sodium	0.50
20.00	6	Natrosol 250M	4.00
30.00	7	Avicel HC 591	6.00
20.00	8	Sodium phosphate dibasic	4.00
7.50	9	Sodium phosphate monobasic	1.50
1.00	10	Lemon flavor	0.20
q.s.	11	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge 40% of item 11 in a stainless steel-jacketed vessel and heat to 90˚ to 95˚C.
2. Add items 2 and 3 and mix to dissolve; cool to 40˚C.
3. Charge item 11 and item 6 in a separate vessel at 70˚ to 80˚C and stir for 30 minutes.
4. Add and disperse item 7 in step 3.
5. Transfer to step 1 and mix to disperse.
6. In a separate vessel add and mix item 4 with items 1 and 11.
7. Add to step 6.
8. Add flavor and bring to volume.

Sulfacetamide Sodium and Sulfur Cleanser and Suspension

Each gram of Plexion (sodium sulfacetamide 10% and sulfur 5%) cleanser contains 100 mg sodium sulfacetamide and 50 mg sulfur in a cleanser base containing water, sodium methyl oleyltaurate, sodium cocoyl isethionate, disodium oleamido MEA sulfosuccinate, cetyl alcohol, glyceryl stearate and PEG-100 stearate, stearyl alcohol, PEG-55 propylene glycol oleate, magnesium aluminum silicate, methylparaben, disodium EDTA, butylated hydroxytoluene, sodium thiosulfate, fragrance, xanthan gum, and propylparaben. Each gram of Plexion (sodium sulfacetamide 10% and sulfur 5%) topical suspension contains 100 mg sodium sulfacetamide and 50 mg sulfur in a topical suspension containing water, propylene glycol, isopropyl myristate, light mineral oil, polysorbate 60, sorbitan monostearate, cetyl alcohol, hydrogenated cocoglycerides, stearyl alcohol, fragrances, benzyl alcohol, glyceryl stearate and PEG-100 stearate, dimethicone, zinc ricinoleate, xanthan gum, disodium EDTA, and sodium thiosulfate.

Sulfadiazine and Trimethoprim Veterinary Oral Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
400.00	1	Sulfadiazine	400.00
80.00	2	Trimethoprim	80.00
50.00	3	Sodium hydroxide	50.00
20.00	4	Kollidon CL-M	20.00
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 3 into a stainless steel vessel along with item 5; mix and dissolve.
2. Add and suspend item 4. Mix well.
3. Add and suspend items 1 and 2; homogenize if necessary.
4. Fill.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
200.00	1	Sulfamethoxazole	40.00
40.00	2	Trimethoprim	8.00
2.50	3	Carrageenan (Hydrogel 843T)	0.50
18.75	4	Tragacanth	3.75
2.50	5	Saccharin sodium dihydrate	0.50
0.625	6	Anise oil	0.125
3.125	7	Methyl paraben	0.625
2.70	8	Propyl paraben	0.54
2.17	9	Alcohol dehydrated	0.435
2914.00	10	Sorbitol solution	582.80
403.75	11	Glycerin	80.75
q.s.	12	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add and disperse Hydrogel 843T in approximately 8 mL purified water.
2. Heat 30 mL purified water to 100˚C and add to dispersion from step 1 with mixing.
3. Let stand overnight.
4. Load trimethoprim and 7 g sulfamethoxazole into a suitable mixer; blend.
5. Moisten blend with approximately 25 mL water.
6. Spread mass as small pancakes onto oven trays and dry at 50˚C for approximately 14 hours.
7. Retain balance of sulfamethoxazole for later use.
8. While mixing, add 75 mL water. Mix until homogenous.
9. Charge approximately 350 mL water into a suitable stainless steel mixing tank. Add and dissolve saccharin with mixing.
10. Add tragacanth and continue mixing for 4 hours.
11. Separately add and dissolve the following ingredients in alcohol: methylparaben, propylparaben, and anise oil.
12. Add solution from step above and sorbitol to the preparation from step 1. Mix for 3 hours and let stand overnight.
13. Add gel from step above with mixing. Mix for approximately 15 minutes.
14. Pass trimethoprim/sulfamethoxazole mass from step 4 and balance of sulfamethoxazole through a 595-micron-aperture screen in Fitzmill knives forward, medium speed, and slowly add to main tank with continuous agitation.
15. Add glycerin to main tank with mixing.
16. Pass the whole batch through a colloid mill until particle size and homogeneity meet specifications. Rinse mill and other equipment with purified water. Add the rinsings to the batch and mix.
17. If necessary, deaerate the product mixing under vacuum (ca. 20 to 25 inches of mercury). Release vacuum and check volume.
18. Bring to volume with water and mix.
19. Stir the suspension until homogeneous. Fill while stirring.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
80.00	1	Sulfamethoxazole	80.00
16.00	2	Trimethoprim	16.00
30.00	3	Kollidon CL-M	30.00
100.00	4	Sucrose	100.00
q.s.	5	Water, purified	q.s. to 1 L
2.00	6	Vanillin	2.00
2.00	7	Flavor chocolate	2.00

MANUFACTURING DIRECTIONS

1. Charge in a suitable stainless steel-jacketed vessel items 4 and 5, heat to dissolve.
2. Cool to 40˚C.
3. Add, after passing through 200-mesh sieve, items 1 to 3 into step 2; mix to dissolve.
4. Add flavors, mix and fill.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
80.00	1	Sulfamethoxazole	80.00
16.00	2	Trimethoprim	16.00
50.00	3	Sucrose	5.00
30.00	4	Lutrol F 127 or Lutrol F 68	30.00
q.s.	5	Water, purified	q.s. to 1 L
q.s.	6	Vanillin	q.s.
q.s.	7	Flavor chocolate	q.s.

MANUFACTURING DIRECTIONS

1. Charge in a suitable stainless steel-jacketed vessel items 3 and 4, heat to dissolve.
2. Cool to 40˚C.
3. Add, after passing through 200-mesh sieve, items 1, 2, and 4 into step 2; mix to dissolve.
4. Add flavors, if used; mix and fill.

Sulfathiazole Veterinary Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
8.00	1	Sulfathiazole	8.00
225.00	2	Kollidon 25	225.00
q.s.	3	Preservative	q.s.
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 4 in a suitable stainless steel-jacketed vessel, heat to 70˚C.
2. Add and disperse item 2.
3. Add and dissolve item 1 to a clear solution
4. Filter, if necessary, and fill.
5. Optionally, an antioxidant such as 0.02% sodium bisulfite or 0.5% cystein may be added if necessary.

Sulfidoxine Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
20.00	1	Sulfidoxine	20.00
680.00	2	Lutrol E 400	680.00
q.s.	3	Preservatives	q.s.
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable stainless steel-jacketed vessel; heat to 60˚C and mix.
2. In a separate vessel charge item 4 and heat to 90˚ to 95˚C and then add item 3 (e.g., parabens) and dissolve; cool to 40˚C.
3. Add step 2 into step 1. Mix to clear solution.

Sulfidoxine and Pyrimethamine Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.70	1	Tylose	2.70
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
600.00	4	Sugar	600.00
0.15	5	Sodium hydroxide	0.15
6.00	6	Trisodium citrate dehydrate	6.00
2.00	7	Benzoic acid	2.00
100.00	8	Sorbitol syrup	100.00
4.00	9	Tween 80	4.00
100.00	10	Sulfadoxine micronized	100.00
5.00	11	Pyrimethamine	5.00
0.20	12	Flavor	0.20
0.20	13	Flavor	0.20
0.20	14	Flavor	0.20
q.s.	15	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Boil a suitable quantity of item 15, cool down to 70˚C, and add and dissolve items 2 and 3.
2. Add item 1 and dissolve in item 15 in a separate container and then add to step 1.
3. In a separate container add and dissolve sodium hydroxide, sodium citrate, and benzoic acid in item 15 and add to step 1.
4. Add and mix sorbitol with Tween 60 and item 10, stir for 15 minutes, and add to step above.
5. Add item 11 to step above and mix to dissolve.
6. Add flavors and bring to volume.

Sumatriptan Nasal Spray

Each Imitrex Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-μL unit-dose aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulfuric acid, sodium hydroxide, and purified water. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742m Osmol for the 5- and 20-mg Imitrex nasal spray, respectively.

MANUFACTURING DIRECTIONS

1. Charge 2.6 g of sumatriptan into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved.
2. After closing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 7 bar (20°C) in another pressure-addition vessel is added with stirring.
3. The preparation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Terfenadine Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
30.00	1	Terfenadine, 8% excess	6.48
2250.00	2	Sucrose	450.00
7.50	3	Sodium methyl paraben	1.50
2.500	4	Sodium propyl paraben	0.50
300.00	5	Propylene glycol	60.00
15.00	6	Polysorbate 80 (Tween 80)	3.00
50.00	7	Benzyl alcohol	10.00
0.24	8	Anise oil	0.048
15.00	9	Magnesium aluminium silicate (Veegum HV)	3.00
125.00	10	Glycerin	25.00
18.74	11	Carboxymethylcellulose sodium	3.74
0.76	12	Citric acid (monohydrate)	0.15
—	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 240.0 g of item 13 to the mixer and heat to 90˚C. Add and dissolve item 2 while mixing.
2. Add and dissolve items 3 and 4 in the mixer at step 1 while mixing at speed 18 to 20 rpm for 15 minutes.
3. Cool down to about 50˚ to 55˚C.
4. Filter the syrup.
5. Collect the syrup in clean stainless steel tank.
6. Clean mixer with item 13 and transfer the filtered syrup from step 4. Maintain temperature at 35˚C.
7. Add 80.0 g of item 13 (70˚C) in a separate stainless steel container and disperse item 9 by using stirrer. Keep aside for 1 hour for hydration.
8. Add item 10 in a separate stainless steel container and disperse item 11 while mixing with stirrer.
9. Add 80.0 g of item 13 (70˚C) while mixing. Make a gel and keep aside.
10. Add 160.0 g of item 13 (60˚C) in a separate stainless steel container.
11. Dissolve item 6. Avoid foam formation. Add item 1 slowly while mixing at slow speed. Add item 5 while mixing at slow speed. Keep the solution aside.
12. Transfer items 9, 11, and 1 dispersions from steps 3, 4, and 5, respectively, to the mixer.
13. Mix at speed 18 rpm for 10 minutes.
14. Mix item 8 in item 7 and add to the mixer. Mix for 2 minutes.
15. Dissolve item 12 in 3.20 g of item 13 and add to the mixer. Mix for 2 minutes.
16. Add cold item 13 (25˚C) to make up the volume to 1.0 L.
17. Homogenize for 10 minutes at high speed under vacuum 0.5 bar, 18 to 20 rpm, temperature 25˚C.
18. Check the dispersion for uniformity.
19. Check the pH (limit 8.0 to 9.0 at 25˚C). If required, adjust the pH with 20% solution of citric acid or sodium citrate.
20. Filter the suspension through a 500-micron sieve to storage tank.

Terfenadine Suspension

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
12.00	1	Terfenadine	12.00
30.00	2	Lutrol F 127	30.00
36.00	3	Cremophor RH 40	36.00
q.s.	4	Preservatives	q.s.
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 5 in a suitable stainless steel-jacketed vessel and heat to 40˚C.
2. Add and dissolve item 2 and 3 in step 1.
3. While stirring, add item 1 and suspend.
4. Homogenize if necessary and fill.

Theophylline Sodium Glycinate Elixir

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
125.00	1	Theophylline Sodium Glycinate[a]	25.00
4000.00	2	Sucrose	800.00
7.50	3	Sodium benzoate	1.50
0.75	4	Saccharin sodium	0.15
0.025	5	FD&C red no. 40	0.005
1.00	6	Flavor	0.20
q.s.	7	Water, purified	q.s. to 1 L

[a]125 mg theophylline sodium glycinate is equivalent to 60 mg theophylline hydrate.

MANUFACTURING DIRECTIONS

1. Add 400.0 g of item 7 to the manufacturing vessel and heat to 95˚ to 98˚C. Add items 3 and 4 to dissolve. Mix for 10 minutes at low speed.
2. Add item 2 while mixing at low speed, temperature 95˚ to 98˚C. When addition is over, mix for 30 minutes at high speed.
3. Cool to 30˚C while mixing at low speed.
4. Add 50.0 g of item 7 (25˚ to 30˚C) in a separate container and dissolve item 1 by using stirrer. Mix for 10 minutes and transfer to the manufacturing vessel at step 3.
5. Rinse the container (step 3) with 1.0 g of item 7 (25˚ to 30˚C) and transfer the rinsings to the manufacturing vessel while mixing at low speed.
6. Dissolve item 5 in 1.0 g of item 7 in a stainless steel container with slow stirring by stirrer. Transfer to the manufacturing vessel while mixing at low speed.
7. Add item 6 to the manufacturing vessel step 4 while mixing. Mix for 10 minutes at low speed.
8. Make up the volume to 1 L with item 7 and, finally, mix for 5 to 10 minutes at high speed.
9. Check and record the pH (limit 8.5 to 9.0 at 25˚C).
10. Filtration: Assemble the filter press. Wash the filters using about 1 L of purified water (25˚) by passing through filters at 0.2 bar. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.
11. Transfer the filtered syrup to the storage vessel.

Thiabendazole Suspension

Mintezol (Thiabendazole) is an anthelmintic provided as a suspension, containing 500 mg thiabendazole per 5 mL. The suspension also contains sorbic acid 0.1% added as a preservative. Inactive ingredients in the tablets are acacia, calcium phosphate, flavors, lactose, magnesium stearate, mannitol, methylcellulose, and sodium saccharin. Inactive ingredients in the suspension are an antifoam agent, flavors, polysorbate, purified water, sorbitol solution, and tragacanth.

Thiothixene Oral Concentrate

The thioxanthenes differ from the phenothiazines by the replacement of nitrogen in the central ring with a carbon-linked side chain fixed in space in a rigid structural configuration. An N,N-dimethyl sulfonamide functional group is bonded to the thioxanthene nucleus. Ingredients are thiothixene (2 to 30 mg/30 mL), alcohol, cherry flavor, dextrose, passion fruit flavor, sorbitol solution, and water.

Timolol Maleate Opthalmic Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
2.50	1	Timolol maleate	2.50
q.s.	2	Vehicle (pluraflo 1220 92.37%, ethanol 2.11%, anhydrous glycerin 5.16%)	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add glycerine, ethanol, and pluraflo to a clean vessel.
2. Add timolol. Cover tightly and stir until a clear solution is obtained.

Tolnafate Foot Care Microemulsion

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
155.00	1	Ethoxydiglycol	155.00
130.00	2	Polyglyceryl-6 dioleate	130.00
450.00	3	PEG-8 caprylic/capric glycerides	450.00
10.00	4	Tolnafate	10.00
100.00	5	Water, purified	100.00
50.00	6	Apricol kernel oil PEG-6 esters	50.00
100.00	7	Caprylic/capric trilgycerides	100.00
5.00	8	Chlorocresol	5.00

MANUFACTURING DIRECTIONS

1. Mix items 1 to 3 and dissolve item 4 in this mixture.
2. Add items 5 to 8 and mix until uniform.

Tolu Balsam Cough Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
11.03	1	Tolu balsam tincture	11.03
2.50	2	Magnesium carbonate	2.50
15.00	3	Sucrose	15.00
q.s.	4	Water, purified	90.000 mL
0.77	5	Methyl paraben	0.77
0.086	6	Propyl paraben	0.086
514.36	7	Sucrose	0.51
129.24	8	Glycerin (96%)	0.13
2.00	9	Dextromethorphan hydrobromide	2.00
1.00	10	Ephedrine HCl[a]	1.00
8.00	11	Ammonium chloride	8.00
0.40	12	Chlorpheniramine maleate	0.40
1.00	13	Phenylephrine hydrochloride	1.00
333.32	14	Glucose liquid	0.33
0.35	15	Flavor	0.35
0.15	16	Flavor	0.15
1.02	17	Ipecac fluid extract	1.01
8.57	18	Alcohol[b]	8.57
0.0375	19	Dye	0.037
q.s.	20	Acid hydrochloric	q.s.
q.s.	21	Water, purified	q.s. to 1 L

[a]May be deleted.

[b]Tolu balsam tincture contains 80% alcohol. Use this item optionally to dissolve flavors.

MANUFACTURING DIRECTIONS

1. Charge Tolu balsam tincture into mixing tank and add magnesium carbonate.
2. Mix well to suspend.
3. Add sugar (item 3) with mixing. Add 90 mL purified water (item 4) and mix thoroughly.
4. Allow to set for 1 hour.
5. Mix periodically while circulating through filter.
6. Solution must be brilliantly clear. Filter and save for next part.
7. Charge 210.5 mL purified water (item 21) into suitable tank.
8. Add and dissolve aseptoforms M and P with heat 90° to 95°C and mixing.
9. Add and dissolve sugar (item 7) with mixing.
10. Heat if necessary. Add glycerine, continue agitation, and cool to room temperature. Add filtrate from step above to cooled syrup.
11. Add and dissolve the following ingredients with mixing: dextromethorphan HBr, ephedrine HCl (if used), ammonium chloride, chlorpheniramine maleate, and phenylephrine HCl.
12. Add glucose. Mix well. Add and dissolve in alcohol: flavors and and ipecac fluid extract.
13. Add to tank, or in a separate container add flavors and ipecac extract to 10 mL glucose liquid, and mix. Add this to the main mixture.
14. Rinse the container with a further 5 mL glucose liquid and add the rinsing to the mixture.
15. Add the remaining glucose liquid. Mix well.
16. Dissolve in 1.75 mL purified water and add.
17. Check pH (range 4.0 to 5.0). Adjust to pH 4.0 to 5.0 with hydrochloric acid.
18. Make the volume to 1 L with purified water.
19. Filter until sparkling clear. Add 0.5 g Hyflo® to mixing tank, mixing until uniform.
20. Filter into tank for filling.

Tretinoin Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.50	1	Tretinoin (BASF)	0.50
140.00	2	Cremophor RH 40	140.00
150.00	3	Propylene glycol	150.00
0.50	4	Butylated hydroxytolune	0.50
1.00	5	Alpha bisabolol natural (BASF)	1.00
q.s.	6	Water, purified	q.s. to 1 L
q.s.	7	Parabens	q.s.
q.s.	8	Sorbic acid	q.s.

MANUFACTURING DIRECTIONS

1. Charge items 1 to 5 in a suitable stainless steel-jacketed vessel; heat to 40˚ to 50˚C to obtain a clear solution.
2. In a separate jacketed vessel, charge item 6 and heat to 90˚ to 95˚C.
3. Add and dissolve items 7 and 8; cool to 40˚C.
4. Add step 3 into step 1.
5. Mix to clear solution.
6. Filter if necessary and fill.

Triamcinolone Acetonide Nasal Spray

Tri-Nasal spray is a metered-dose manual-spray pump in an amber polyethylene terephthalate bottle with 0.05% w/v triamcinolone acetonide in a solution containing citric acid, edetate disodium, polyethylene glycol 3350, propylene glycol, purified water, sodium citrate, and 0.01% benzalkonium chloride as a preservative. Tri-Nasal Spray pH is 5.3.

MANUFACTURING DIRECTIONS

Dissolve 20 g triamcinolone acetonide in 1.5 kg ethanol. The solution is dispensed into open aluminum containers, and these are sealed with suitable metering valves. The containers are filled by means of the pressure-filling technique with a total of 4 kg of HFA 227 that has been aerated with carbon dioxide and adjusted to a pressure of 5 bar (20˚C).

Triclosan Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Vehicle (pluronic F108 55.80%, ethanol 21.30%, water 22.90%)	q.s. to 1 L
2.80	2	Triclosan monophosphate	2.80
10.00	3	Menthol	10.00
1.00	4	Sodium saccharin	1.00
0.50	5	Monosodium glycerhizzinate	0.50
q.s.	6	Flavors and colors	q.s.

MANUFACTURING DIRECTIONS

1. Mill and screen the menthol and triclosan monophosphate to reduce particle size.
2. Add the menthol, triclosan monophophate, sodium saccharin, and monoammonium glycerizzinate into a clean vessel.
3. Add propylene glycol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Triprolidine and Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.25	1	Triprolidine HCl, 4.8% excess	0.26
6.00	2	Pseudoephedrine HCl, 3.0% excess	6.18
600.00	3	Sucrose	600.00
100.00	4	Glycerin (glycerol)	100.00
100.00	5	Sorbitol (70% solution)	100.00
15.00	6	Propylene glycol	15.00
1.00	7	Methyl paraben	1.00
0.30	8	Propyl paraben	0.30
0.50	9	Saccharin sodium	0.50
0.04	10	Quinoline yellow	0.04
0.05	11	Menthol	0.05
0.25	12	Raspberry flavor	0.25
1.15	13	Sodium citrate	1.15
q.s.	14	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Add 400.0 g of item 14 to the manufacturing vessel and heat to 90˚ to 95˚C.
2. Add items 7 and 8 while mixing to dissolve at high speed.
3. Add item 3 while mixing at slow speed. Temperature 90˚ to 95˚C.
4. Mix for 1 hour at high speed. Cool down to 50˚C while mixing at slow speed.
5. Add items 9 and 13 to the manufacturing vessel while mixing at high speed.
6. Load items 5 and 4 into the manufacturing vessel using transfer pump while mixing at high speed.
7. Add 20.0 g of cold item 14 (30˚C) in a separate container and dissolve items 1 and 2 by using stirrer.
8. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
9. Add 1.0 g of item 14 in a separate container and dissolve item 10 manually.
10. Add color to the manufacturing vessel while mixing at high speed. Dissolve item 11 in item 12. Then add item 6 to it. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
11. Make up the volume 1 L with item 14 and, finally, mix for 15 to 20 minutes at high speed.
12. Check and record the pH (limit 5.8 to 6.8 at 25˚C).
13. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.

Tulobuterol Syrup

Bill of Materials			
Scale (mg/5 mL)	**Item**	**Material Name**	**Quantity/L (g)**
1.00	1	Tulobuterol hydrochloride	0.20
5.00	2	Water, purified	100.00 mL
3.75	3	Glycerin	75.00 mL
0.03	4	Methyl paraben	0.60
0.0075	5	Propyl paraben	0.15
q.s.	6	Red dye	25.00 mg
q.s.	7	Flavor	5.00
q.s.	8	Sorbitol (70%)	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat 50 mL water to about 80˚C and 95˚C in a suitable vessel.
2. Add the methylparaben and propylparaben. Rinse the containers with some of the remaining water if necessary. Stir until dissolved, maintaining temperature at about 80˚C.
3. Warm about 340 mL sorbitol solutiion to 40˚C and 55˚C in a suitable vessel.
4. Transfer the warm sorbitol to the final mixing vessel and add the hot paraben solution from step 2, stirring continuously. Rinse paraben solution container with 5 mL hot water and add to the bulk.
5. Dissolve tulobuterol and the dye in about 25 mL remaining water, rinsing the containers with some of the remaining water if necessary.
6. Add the solution from step above to the final vessel, mixing continuously. It is important to ensure all of the colored solution is transferred. Rinse the container with a portion of the remaining water.
7. Add the glycerol and flavor to the bulk solution. Rinse the glycerol container with the remaining water and add to the bulk. Make up to volume with the sorbitol solution.
8. Mix gently until a uniform syrup is obtained, avoiding incorporation of air bubbles.
9. If necessary, circulate through a filter press until sparkling clear.
10. Pass filtered clear syrup into a suitable holding tank.

Undecylenic Acid and Chloroxylenol Solution

This is an antifungal solution for topical use containing 25% undecylenic acid and 3% chloroxylenol as its active ingredients in a penetrating oil base. Available in 1-ounce bottles with special brush applicator.

Urea Peroxide Ear Drops

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
65.00	1	Urea peroxide, 40% excess	91.000
15.00	2	Sodium citrate dihydrate	15.000
5.00	3	Polysorbate 20	5.000
2.50	4	Acid tartaric	2.500
q.s.	5	Glycerin anhydrous	q.s
q.s.	6	Nitrogen gas	q.s

MANUFACTURING DIRECTIONS

1. Add 500 mL glycerin into a suitable tank.
2. Start mixing at slow speed and heat the contents to 70˚ to 75˚C.
3. Flood tank with nitrogen, increase mixing speed and slowly add sodium citrate. Add tartaric acid. Mix for at least 30 minutes or until dissolved.
4. Maintain the temperature at 70˚ to 75˚C. When sodium citrate is completely dissolved, cool to 25˚ to 30˚C with constant mixing.
5. Prepare urea peroxide by breaking lumps and screening to remove large particles. Use gloved hands.
6. Add an additional 250 to 300 mL glycerin into tank.
7. Add urea peroxide slowly to prevent lumping, while constantly mixing.
8. Mix at high speed after addition.
9. Add polysorbate 20 with constant mixing.
10. Bring to final volume with glycerin.
11. Mix for at least 30 minutes and until solution is clear.
12. Pass solution through an approximately 100-mesh (150-micron aperture, or similar) screen and collect in clean, dry sealable vessel. The solution is too viscous to flow through a membrane or any cellulosic filter.

Valproic Acid Capsules

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. Ingredients for the 250 mg capsules are corn oil, FD&C yellow no. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide.

Valproic Acid Syrup

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Capsules and syrup are antiepileptics for oral administration. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. Inactive ingredients are FD&C red no. 40, glycerin, methylparaben, propylparaben, sorbitol, sucrose, water, and natural and artificial flavors.

Vancomycin Hydrochloride Oral Solution

Vancocin HCl for oral solution contains vancomycin hydrochloride equivalent to 10 g (6.7 mmol) or 1 g (0.67 mmol) vancomycin. Calcium disodium edetate, equivalent to 0.2 mg edetate per gram of vancomycin, is added at the time of manufacture. The 10-g bottle may contain up to 40 mg of ethanol per gram of vancomycin.

Vitamin A and D Infant Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
1500 U	1	Vitamin A palmitate 1.7 million U/g, 50% excess	1.32
400 U	2	Vitamin D 40 MU/g (Cholecalciferol), 25% excess	0.0125
10.00	3	Polysorbate 80 (Tween 80)	10.00
0.88	4	Vitamin E oil (alpha-tocopheryl acetate)	0.88
0.50	5	Edatate disodium (sodium EDTA)	0.50
1.00	6	Ascorbic acid	1.00
0.100	7	Saccharin sodium	0.10
600.00	8	Glycerin (glycerol)	600.00
100.00	9	Sorbitol (70% solution)	10000
50.00	10	Propylene glycol	50.00
1.00	11	Flavor	1.00
1.50	12	Flavor	1.50
0.02	13	Dye	0.02
0.003	14	Dye	0.003
—	15	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS.

1. Collect 200.0 g of item 15 in melting vessel.
2. Heat to 90° to 95°C for 10 minutes and then cool to 20° to 25°C.
3. Bubble nitrogen gas into item 15 for 20 minutes.
4. Load 100.0 g of item 15 to the manufacturing vessel.
5. Bubble nitrogen gas during all stages of the processing.
6. Add items 5, 6, and 7, one by one, to the manufacturing vessel while mixing.
7. Check that all materials are dissolved completely.
8. Add items 8 and 9 and 20.0 g of item 10, one by one, to the manufacturing vessel while mixing at slow speed. Mix for 5 minutes. Avoid aeration.
9. Add item 3 in a stainless steel container.
10. Mix items 1, 2, and 4, one by one, using stirrer. Mix for 1 hour at slow speed. Avoid aeration.
11. Add oil phase to the aqueous phase in the manufacturing vessel at a rate of 4 mL per minute while mixing, continuing to bubble nitrogen gas, throughout the process.
12. Dissolve items 11 and 12 in 30.0 g of item 10 in a stainless steel container by slow stirring. Add into manufacturing vessel while mixing.
13. Dissolve items 14 and 13 in 40.0 g of item 15 (25° to 30°C) in a stainless steel container by slow stirring.
14. Add into manufacturing vessel while mixing.
15. Adjust the volume to 1.0 L with cooled item 15.
16. Check and record the volume and pH (limit between 2.5 and 4.8).
17. Filter the solution through a prefilter and a membrane filter of 0.2 micron into the receiving tank.
18. Bubble with nitrogen gas for 15 minutes. Store the solution with nitrogen blanket.

Vitamin A and Vitamin D3 Drops

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/L. (g)**
30,000 U	1	Vitamin A palmitate 1.7 million U/g	1.90
3000 U	2	Vitamin D3 40 million U/g	7.5 mg
12.0	3	Cremophor RH 40	12.00
0.3	4	Butylhydroxytoluene	0.30
10.0	5	Lutrol E 400	10.00
0.8	6	Parabens (propyl and methyl)	0.80
0.2	7	Sorbic acid	0.20
74.8	8	Water, purified	74.80

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 to 5 and solution of items 6 to 8 to about 65˚C.
2. Add this slowly to the well-stirred mixture of items 1 to 5. Yellow clear or slightly opalescent liquid is obtained.

Vitamin A and Vitamin D3 Oral Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (mg)**
1000 U	1	Vitamin A palmitate 1.7 million U/g	60.00
100 U	2	Vitamin D3 40 million U/g	0.30
0.002	3	Butylhydroxytoluene	0.20
3.00	4	Cremophor EL or Cremophor RH 40	3000.00
q.s.	5	Preservative	q.s
q.s.	6	Flavor	q.s
q.s.	7	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 to 4 to about 65˚C; stir well
2. Add slowly the hot solution of item 5 (65˚C).
3. Cool to room temperature and add item 6. A clear, yellow liquid is formed.

Vitamin A and Vitamin D3 Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
30,000 U	1	Vitamin A palmitate 1.7 million U/g	19.00
10,000 U	2	Vitamin D3 40 million U/g	0.25
70.00	3	Cremophor RH 40	7.0
q.s.	4	Sugar syrup 50%	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat mixture of items 1 to 3 to about 45˚C; stir well.
2. Add slowly the item 4. A clear, yellow liquid with pH 6.2 is formed.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
25,000 U	1	Vitamin A palmitate 1.7 million U/g	15.00
50.00	2	Vitamin E acetate	50.00
210.00	3	Cremophor RH 40[a]	210.00
q.s.	5	Preservative	q.s
q.s.	6	Water, purified	q.s. to 1 L

[a]The quantity is reduced by 1.0 G if DL-alpha-tocopherol is also added at 1.0-g level in the formulation.

MANUFACTURING DIRECTIONS

1. Mix the vitamins with Cremophor RH 40 (and DL-alpha-tocopherol, if used) at 60°C.
2. Add solution of preservatives (at 37°C) slowly, with stirring. Clear, yellow, viscous liquids are formed.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
5000 U	1	Vitamin A palmitate 1.7 million U/g	3.33
50.00	2	Vitamin E acetate	60.00
150.00	3	Cremophor RH 40	150.00
150.00	4	Alcohol	150.00
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat mixture items 1 to 3 to about 65°C, stir well.
2. Slowly add the mixture of items 4 and 5. Color is yellow, and clarity should be clear (turbity units: 25 FTU). It must be tested to see whether the ethanol concentration has a sufficient preservative efficiency. The addition of butylhydroxytoluene as antioxidant is recommended.

Vitamin A Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (g)**
100,000 U	1	Vitamin A palmitate 1.7 million U/g	65.00
2.00	2	Butylhydroxytoluene	2.00
210.00	3	Cremophor RH 40	210.00
q.s.	4	Preservative	q.s
q.s.	5	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1 to 3 to about 65°C; stir well.
2. Add very slowly the warm solution of items 4 and 5 (65°C). Clear, yellow liquid, miscible with water, is formed.

Vitamin A Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50,000 U	1	Vitamin A palmitate 1.7 million U/g	30.00
110.00	2	Cremophor RH 40	110.00
1.00	3	Butylhydoxytoluene	1.00
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Heat the mixture of items 1 to 3 to about 65˚C; stir very well.
2. Add slowly the hot water (65˚C). The solution should be yellow and clear or slightly opalescent and of low viscosity. Lutrol E 400 can be added at a level of 5%; compensated by item 4.

Vitamin B-Complex Syrup

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.600	1	Thiamine hydrochloride	0.600
0.550	2	Riboflavin 5-phosphate sodium	0.550
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.550	5	Pyridoxine hydrochloride	0.550
2.00	6	Sorbic acid	2.00
0.05	7	EDTA sodium	0.05
2.25	8	Vanillin	2.25
465.00	9	Sucrose	465.00
25.00	10	Kollidon 25	25.00
90.00	11	Glycerol	90.00
100.00	12	Propylene glycol pharma	100.00
310.00	13	Water, purified	310.00

MANUFACTURING DIRECTIONS

1. Dissolve the sucrose in the heat mixture of glycerol, propylene glycol and water; cool to room temperature.
2. Dissolve the other components to obtain a clear solution.

Vitamin B-Complex Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.66	1	Dexpanthenol	0.66
4.40	2	Nicotinamide	4.44
0.22	3	Pyridoxine HCl	0.22
0.60	4	Riboflavin-5-phosphate sodium	0.60
1.50	5	Thiamine HCl	1.50
350.00	6	Sorbitol (70% solution)	350.00
11.20	7	Propylene glycol	11.20
0.84	8	Methyl paraben	0.84
0.16	9	Propyl paraben	0.16
550.00	10	Maltitol solution (lycasin 80/55)	550.00
0.15	11	Edetate disodium (sodium EDTA)	0.15
3.72	12	Citric acid (monohydrate)	3.72
3.72	13	Sodium citrate	3.72
2.50	14	Sodium benzoate	2.50
0.50	15	Saccharin sodium	0.50
150.00	16	Glycerin (glycerol)	150.00
1.50	17	Flavor	1.50
1.00	18	Flavor	1.00
—	19	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Load items 6, 10, and 16 in a suitable manufacturing vessel and mix for 5 minutes.
2. Dissolve items 8 and 9 in item 7 in a stainless steel container.
3. Put the whole container in hot water (60° to 70°C) and stir to dissolve.
4. Add the clear solution to mixer.
5. Dissolve items 11 and 12 in 40.0 g of item 19 in a stainless steel container.
6. Add the clear solution to mixer.
7. Dissolve items 14, 13, and 15 in 50.0 g of item 19 in a stainless steel container. Add the clear solution to mixer and mix for 5 minutes.
8. Dissolve item 1 in 10.0 g of item 19 in a stainless steel container.
9. Add the clear solution to mixer. Dissolve items 5 and 3 in 10.0 g of item 19 in a stainless steel container. Add the clear solution to mixer.
10. Dissolve items 2 and 4 in 30.0 g of item 19 in a stainless steel container.
11. Add the clear yellow solution to mixer and mix for 5 minutes.
12. Add items 17 and 18 to mixer. Make up the volume up to 1 L with item 19 and finally mix for 15 to 20 minutes.
13. Check and record the pH (limit 4.4 to 4.8 at 25°C). If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 200 to 300 mL syrup.
15. Transfer the filtered syrup to the storage vessel, flushing with nitrogen gas. Store the syrup under nitrogen blanket not more than 2 days before filling.

Vitamin B-Complex Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.60	1	Thiamine hydrochloride (BASF)	0.60
0.55	2	Riboflavin 5-phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
12.00	4	Dexpanthenol (BASF)	12.00
0.55	5	Pyridoxine hydrochloride	5.50
2.00	6	Sorbic acid	20.00
0.050	7	EDTA sodium	0.50
2.25	8	Vanillin	22.50
465.00	9	Sucrose	465.00
25.00	10	Kollidon 25	25.00
90.00	11	Glycerin	90.00
100.00	12	Propylene glycol	100.00
q.s.	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge glycerin, propylene glycol, and purified water in a suitable stainless steel-jacketed vessel; heat to 65˚C.
2. Add and dissolve sucrose in step 1.
3. Cool to room temperature.
4. Add and dissolve all other items.
5. Filter if necessary. Fill.

Vitamin B-Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.150	1	Thiamine hydrochloride	0.15
0.15	2	Riboflavin phosphate sodium	0.15
0.70	3	Nicotinamide	0.70
0.035	4	Dexpanthenol	0.035
0.15	5	Pyridoxine hydrochloride	0.15
2.25	6	Ascorbic acid, crystalline	2.25
0.28	7	Orange aroma	0.28
0.56	8	EDTA sodium	0.56
186.50	9	Propylene glycol Pharma + water (2:1)	186.50
0.15	10	Parabens	0.155
84.30	11	Sorbitol, crystalline	84.30
562.50	12	Sucrose, crystalline	562.50
q.s.	13	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Dissolve items 1 to 8 in item 2.
2. Prepare solution of items 10 to 13 by heating, cool and mix with solution balance of formulation.
3. Adjust to pH 4.2 to 4.5. Adjust volume with item 13; use more if necessary. Use nitrogen as inert gas during packaging.

Vitamin B-Complex (without B12) Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
570.00	1	Sucrose	570.00
70.00	2	Glycerin	70.00
3.72	3	Citric acid (monohydrate)	3.72
1.00	4	Edetate disodium (sodium EDTA)	1.00
0.90	5	Calcium pantothenate, 10% excess	1.00
5.70	6	Sodium citrate	5.70
0.84	7	Methyl paraben	0.84
0.18	8	Propyl paraben	0.16
1.90	9	Benzoic acid	1.90
1.14	10	Strawberry flavor manefils	1.14
9.60	11	Alcohol	9.60
1.50	12	Thiamine HCl, 50% excess	1.50
0.20	13	Pyridoxine hydrochloride, 10% excess	0.22
4.00	14	Nicotinamide, 10% excess	4.40
0.30	15	Riboflavin sodium phosphate, 50% excess	0.60
—	16	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Flush with nitrogen gas (purity 99.95%).
2. Add 400.0 g of item 16 to the manufacturing vessel and heat to 90° to 95°C.
3. Add item 1 while mixing at low speed. After addition of item 1 mix for 30 to 35 minutes at high speed and temperature 90° to 95°C.
4. Cool to 40°C while mixing at low speed.
5. Disperse 1.0 g filter aid in 10.0 g cooled item 16 (25° to 30°C) in a stainless steel container to prepare a slurry.
6. Add the slurry to syrup in syrup vessel. Mix for 15 minutes at high speed.
7. Filter the syrup at 1.5 bar.
8. Recirculate about 40 to 60 mL syrup.
9. Transfer the filtered syrup to the storage vessel. Recharge the filtered syrup to the manufacturing vessel. Start mixing.
10. Add item 2 to the syrup vessel while mixing at high speed.
11. Add item 3 to the syrup vessel while mixing to dissolve at high speed.
12. Dissolve item 4 in 6.0 g of cooled item 16 (25° to 30°C) and add to the syrup vessel while mixing at high speed.
13. Dissolve item 5 in 6.0 g of cooled item 16 and add to the syrup vessel while mixing at high speed for 30 minutes.
14. Dissolve item 6 in 10.0 g of cooled item 16 (25° to 30°C) and add to the syrup vessel while mixing at high speed.
15. Dissolve items 7, 8, 9, and 10 in item 11 in a stainless steel container and add to the syrup vessel while mixing at high speed for 15 minutes.
16. Dissolve items 12 and 13 in 6.0 g of cooled item 16 (25° to 30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
17. Rinse the container with 1.0 g of cooled item 16 (25° to 30°C) and add the rinsing to the syrup vessel while mixing at high speed.
18. Flush the vessel with nitrogen gas purity 99.95% for 15 minutes.
19. Dissolve item 14 in 9.0 g of cooled item 16 in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
20. Rinse the container with 1.0 g of cooled item 16 (25° to 30°C) and add the rinsing to the syrup vessel while mixing at high speed.
21. Dissolve item 15 in 4.0 g of cooled item 16 (25° to 30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
22. Rinse the container with 1.0 g of cooled item 16 and add the rinsing to the syrup vessel while mixing at high speed.
23. Make up the volume to 1 L with cooled item 16 (25° to 30°C) and finally mix for 15 minutes at high speed.
24. Check and record the pH. Limit 4.3 to 4.7 at 25°C.

25. If required, adjust pH with 10% solution of citric acid or sodium citrate.
26. Flush the syrup with nitrogen gas purity 99.95% for 15 minutes.
27. Close the tank. Hold the syrup for 12 hours. Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup.
28. Transfer the filtered syrup to the storage vessel.

Vitamin B-Complex, A, C, D, and Calcium Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (g)**
675.00	1	Glycerin	675.00
16.66	2	Niacinamide powder white	16.66
2.739	3	Riboflavin-5′-phosphate sodium, 3% excess	2.822
0.500	4	Methyl paraben	0.500
1.0	5	Acid benzoic	1.00
105.0	6	Saccharin sodium powder	105.00
73.360	7	Calcium chloride granules (dihydrate)	73.36
28.785	8	Ferrous gluconate	28.78
2.25	9	Thiamine HCl powder regular, 35% excess	3.37
1.000	10	Pyridoxine hydrochloride	1.00
83.33	11	Acid ascorbic white powder, 35% excess	112.50
0.258	12	Oil orange terpeneless	0.25
0.081	13	Alcohol	0.081
80.00	14	Polysorbate 80	80.00
0.167	15	Butylated hydroxyanisole	0.16
0.666	16	Viosterol in corn oil (synthetic oleovitamin D USP 1000 mD/g), 25% excess	0.83
0.056	17	Vitamin A palmitate 1,500,000 U/g	0.056
10.000	18	Carmel acid proof	10.00
q.s.	19	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

Product must not stand more than 1 week before filling. Avoid unnecessary exposure of product to light, air, and heat. Manufacture and store product under complete CO_2 protection. Avoid vigorous mixing.

1. Charge glycerin and 210 mL purified water into a stainless steel-jacketed tank.
2. Add with mixing in the following order: niacinamide, riboflavin-5′-phosphate sodium, methylparaben, benzoic acid, and saccharin sodium.
3. Continue mixing and heat to 95° to 100°C and hold to completely dissolve the ingredients.
4. Add, in portions, calcium chloride and stir until complete solution.
5. Continue mixing and cool to 70° to 75°C. Add with mixing and dissolve ferrous gluconate at 70° to 75°C. Check for absence of nondissolved material.
6. Check volume if necessary replace the purified water lost by heating with additional purified water, previously boiled, q.s. to 750 mL.
7. Cool with mixing to room temperature 25° to 30°C while bubbling CO_2 gas through. Continue the CO_2 gas bubbling for balance of process.
8. Add and dissolve each ingredient in the order named: thiamine HCl, pyridoxine HCl, and ascorbic acid. Dissolve oil orange in ethyl alcohol and add with stirring.
9. Heat polysorbate 80 to 50° to 60°C and hold for approximately 10 minutes with slow mixing.
10. Add and dissolve butylated hydroxyanisole.
11. Mix slowly and saturate with CO_2 while cooling to 25° to 30°C.
12. Add and dissolve viosterol in corn oil and vitamin A palmitate, mixing well with CO_2 gas blowing.
13. Add polysorbate solution to main batch and mix thoroughly. Rinse container with a portion of main batch.
14. Heat 50 mL purified water to 35° to 40°C while bubbling CO_2 gas through.
15. Add caramel color. Mix well until uniform.
16. Add to main batch. Rinse container with a small quantity of purified water that has been previously saturated with CO_2 gas.
17. Add to main batch. Add purified water that has been previously saturated with CO_2 gas.
18. Bring to volume.
19. Filter, without using filter aid; cycle to achieve clarity. Keep carbon dioxide cover.

Vitamin B-Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.170	3	Methyl paraben	0.170
1.500	4	Niacinamide powder white	1.500
0.300	5	Riboflavin	0.300
103.600	6	Propylene glycol	103.60
126.400	7	Glycerin	126.40
26.132	8	Iron sulfate granular	26.13
0.0375	9	Dye	0.037
0.250	10	Pyridoxine hydrochloride	0.25
1.200	11	Saccharin sodium powder dihydrate	1.20
22.000	12	Sodium cyclamate powder	22.00
30.000	13	Acid ascorbic white powder	30.00
0.800 g	14	Sodium bicarbonate	0.80
0.360	15	Thiamine hydrochloride powder regular	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol FCC)	0.62
0.0020	17	Vitamin B12 mcg (cyanocobalamine)	2.00 mg
0.007	18	Flavor	0.700 mL
q.s.	19	Water, purified	q.s. to 1 L
q.s.	20	Filter aid hyflo	q.s
q.s.	21	Acid hydrochloric	q.s
q.s.	22	Sodium hydroxide	q.s

MANUFACTURING DIRECTIONS

1. Manufacture under complete CO_2 protection.
2. Load 780 g (portion of item 2) of sorbitol solution into a stainless steel-jacketed tank. Remaining sorbitol to be used later.
3. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution.
4. Heat solution to 85° to 90°C and mix until the ingredients are dissolved.
5. Remove heat. While mixing, cool the main solution to 50° to 60°C.
6. Hold at this temperature while bubbling CO_2 into it. CO_2 protection is continued for the remainder of the manufacturing procedure.
7. Heat 50 mL purified water to boiling and bubble CO_2 into it while cooling to 55°C.
8. Add and dissolve, with mixing, iron sulfate with 30 mL purified water at 55°C. Use CO_2 protection.
9. Warm the solution to 50° to 55°C while mixing to dissolve. Then add the solution slowly, with good mixing, to the solution.
10. The above addition should be made as soon as possible to prevent oxidation. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
11. Cool the solution to 30°C. Add the ascorbic acid with good stirring to 78 g of reserved sorbitol; make a slurry. Use a container that has plenty of headspace.
12. Add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry with stirring until all of the powder has been added and most of the foaming has stopped.
13. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.
14. Rinse the mixing container with 22 g of the reserved sorbitol and add to the product with stirring.
15. Add and dissolve thiamine hydrochloride with mixing. If necessary, warm the D-Pantothenyl alcohol until liquefied and add it to the 0.5 mL CO_2-saturated purified water.
16. Use an additional 0.5 mL CO_2-saturated purified water to thoroughly rinse the container of D-Pantothenyl alcohol and add this to the D-Pantothenyl alcohol solution.
17. Mix the D-Pantothenyl alcohol solution thoroughly until homogeneously dispersed.

18. Add the D-Pantothenyl alcohol solution to the main solution with mixing. Use an additional 0.5 mL CO_2-saturated purified water to rinse out the container in which the D-Pantothenyl alcohol solution was made, and add to the product with mixing.
19. Dissolve the vitamin B12 in 0.5 mL purified water to make a clear solution, and add this solution to the product with good mixing.
20. Dissolve the flavor in the 10 g of propylene glycol, reserved from step above, with good stirring. Add this solution to the product with good mixing. Check pH (range 3.00 to 3.30). Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results.
21. Adjust the volume of the product with the remaining 30 g of the sorbitol solution or, if necessary, purified water to 1 L.
22. Mix for 1 hour. Allow to stand overnight to eliminate entrapped CO_2 gas. Readjust volume to 1 L with purified water. Mix for 1 hour. Filter by adding hyflo filter aid and mixing it, followed by passing through filter press. Do not allow temperature to exceed 30˚C. Bubble CO_2 gas into clear filterate for 5 minutes. Then seal tank and hold product under CO_2 protection.

Vitamin B-Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Quantity/kg (g)**
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
9.00	6	Ascorbic acid, crystalline	9.00
0.25	7	Orange Flavor	0.25
0.05	8	EDTA sodium	0.05
0.50	9	Propyl gallate	0.50
2.00	10	Sorbic acid	2.00
5.00	11	Kollidon 25	5.00
10.00	12	Sorbitol, crystalline	10.00
9.00	13	Glycerol	9.00
10.00	14	1,2-Propylenglycol Pharma	10.00
5.00	15	Water, purified	5.00
60.00	16	Sugar syrup (64% sucrose in water)	60.00

MANUFACTURING DIRECTIONS

1. Mix solution of items 1 to 5 with sugar syrup.
2. Adjust the clear solution to about pH 4.2.
3. Use nitrogen as an inert gas in the final packaging. 10 g provides two to three times the recommended daily allowance.

Vitamin B-Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Glucose liquid	q.s. to 1 L
225.00	2	Water, purified	225.00
0.300	3	Methyl paraben	0.30
1.00	4	Acid benzoic	1.00
5.00	5	Alcohol	5.00
10.00	6	Nicotinamide niacinamide	10.00
10.00	7	Riboflavin USE riboflavin 5 phosphate sodium	1.64
2.00	8	Pyridoxine hydrochloride	2.00
20.00	9	Acid ascorbic	28.00
0.030	10	Dye	0.030
0.020	11	Dye	0.020
2.00	12	Thiamine hydrochloride	2.40
2.00	13	D-Pantothenyl alcohol	2.50
2.00 mcg	14	Vitamin B12 (cyanocobalamine)	0.0034
200.00	15	Sucrose	200.00
0.028 mL	16	Flavor	2.80 mL
q.s.	17	Acid hydrochloric	2.00 mL
q.s.	18	Carbon dioxide gas	q.s.

MANUFACTURING DIRECTIONS

This preparation is susceptible to oxidation and must be protected from air and sunlight at all times. Carbon dioxide must be used extensively to prevent oxygen reacting with the materials. All purified water must be boiled for 10 minutes before use and cooled under carbon dioxide protection.

1. Charge 100 mL purified water into a suitably sized stainless steel tank.
2. Add the riboflavin, nicotinamide, acid benzoic, and paraben.
3. Rinse the tank down with 10 mL purified water, seal, and heat with mixing to 95°C. Continue mixing and heating for 15 minutes until solution is complete. Commence cooling with continuous mixing.
4. When the solution has cooled to 50° to 70°C, add and dissolve the sugar. Commence CO_2 protection when the temperature reaches 40°C.
5. Slurry the ascorbic acid in 75.0 or 110.0 mL (use the smaller quantity only if using a total of 225.0 mL water) CO_2-saturated purified water, and add to bulk solution when temperature has reached 25° to 35°C.
6. Rinse the ascorbic acid vessel with 10.0 mL purified water and add rinsing to bulk. Mix for at least 30 minutes.
7. Dissolve thiamine and pyridoxine in 20.0 mL CO_2-saturated purified water and add to bulk solution at 25° to 35°C.
8. Add 10.0 mL CO_2-saturated purified water to the D-Pantothenyl alcohol and warm on a water bath until solution is complete.
9. Add vitamin B12 and mix until dissolved. Add and dissolve dyes. Add this solution to the bulk solution and mix thoroughly.
10. Mix flavor with 95% of the alcohol and add to the bulk solution. Rinse the container with the remaining alcohol and add to the bulk with vigorous agitation.
11. Check pH (range 3.0 to 3.3). Use hydrochloric acid to adjust if necessary. Adjust the final volume with liquid glucose.
12. Filter through suitable medium until clear and bright.

Vitamin B-Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/L (g)**
q.s.	1	Sorbitol solution	q.s. to 1 L
q.s.	2	Water, purified	225.00
0.200	3	Methyl paraben	0.20
0.200	4	Propyl paraben	0.02
2.00	5	Nicotinamide niacinamide powder white	10.00
10.00	6	Riboflavin, USE riboflavin 5 phosphate sodium	1.64
10.00	7	Iron sulfate (ferrous sulfate) granular	10.000 g
3.60	8	Saccharin sodium powder	3.60
2.00	9	Pyridoxine hydrochloride	2.00
25.00	10	Acid ascorbic	28.00
0.030	11	Dye	0.030
0.020	12	Dye	0.020
2.00	13	Thiamine hydrochloride	2.40
2.00	14	D-Pantothenyl alcohol	2.50
2.0 mcg	15	Vitamin B12 (cyanocobalamine)	0.0034
1.00	16	Flavor	1.00
10.00	17	Propylene glycol	10.00
q.s.	18	Acid hydrochloric	2.00 mL
q.s.	19	Filter aid hyflo	1.00
q.s.	20	Carbon dioxide gas	q.s.

MANUFACTURING DIRECTIONS

This preparation is susceptible to oxidation and must be protected from air and sunlight at all times. Carbon dioxide must be used extensively to prevent oxygen reacting with the materials. All purified water must be boiled for 10 minutes before use and cooled under carbon dioxide protection.

1. Charge 950 g sorbitol solution in a stainless steel–jacketed tank and heat to 95° to 100°C.
2. Heat 250 mL purified water to boiling for 10 minutes and bubble CO_2 into it while cooling to room temperature.
3. Add with stirring parabens, niacinamide, and riboflavin 5 phosphate sodium. Rinse the container with 5 mL water. Stir well. Mix until in solution.
4. Check the clarity. Remove the source of heat from the vessel.
5. Thoroughly deoxygenate the liquid by bubbling CO_2 through the liquid and allow to cool to 50° to 60°C.
6. Heat 15 mL water to 70°C, saturate with CO_2, dissolve saccharin sodium (item 11) and pyridoxine hydrochloride in 5 mL water, and add to the main bulk. Rinse the container with 2.5 mL water.
7. Cool the solution to 30°C with CO_2 protection.
8. Dissolve ascorbic acid in 120 mL water. Rinse the container with 5 mL water.
9. Dissolve dyes in 3 mL water. Rinse the container with 2 mL water. Mix dye solution with ascorbic acid solution. Add this to the main bulk with stirring.
10. Dissolve thiamine in 30 mL water and add to the main bulk. Rinse the container with 2.5 mL water.
11. Add 10 mL water to D-Pantothenyl and warm up on a water bath until in solution. Add this to the main bulk.
12. Rinse the container with 2.5 mL water. Dissolve vitamin B12 in 12.5 mL water and add this to the main bulk.
13. Rinse the container with 2.5 mL water. Mix flavor with 7.5 g propylene glycol until homogeneous, and add this to the main bulk.
14. Rinse the container with 2.5 g propylene glycol and add to the main bulk with vigorous agitation.
15. Check pH (range 3.0 to 3.3). Use hydrochloric acid to adjust if necessary.
16. Adjust the volume of the product with sorbitol solution and mix for 30 minutes to ensure homogeneity. Add hyflo filter aid and mix.
17. Filter the liquid through a filter press previously washed in purified water. Transfer the clear fil-

trate into a clean closed vessel. Mix for 15 minutes while bubbling CO_2 gas.

Vitamin B-Complex, A, C, and D Syrup

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
60.00	1	Sucrose	600.00
51.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
1.00	4	Edatate disodium	1.00
10.00	5	Ascorbic acid, 50% excess	15.00
0.80	6	Sodium hydroxide	0.80
4.00	7	Nicotinamide, 5% excess	4.20
0.40	8	Riboflavin sodium phosphate, 8% excess	0.43
1.00	9	Thiamine hydrochloride, 50% excess	1.50
1.20	10	Pyridoxine hydrochloride, 10% excess	1.32
0.50	11	Monosodium glutamate	0.50
1.26 mcg	12	Cyanocobalamine, 50% excess	0.0018
150.00	13	Propylene glycol	150.00
1000.0 U	14	Vitamin A palmitate 1.75 million/g, 54% excess	0.88
100.0 U	15	Cholecalciferol 40 million/g, 52% excess	0.0038
13.20	16	Polysorbate 80	13.20
2.50	17	Poloxyl 20 cetostearyl ether	2.50
0.30	18	Lemon oil terpenless	0.30
0.84	19	Strawberry oil composed	0.84
—	20	Purified water	q.s. to 1 L

MANUFACTURING DIRECTIONS

This product is an aqueous solution of water-soluble vitamins with oily vitamin A palmitate and cholecalceferol solubilized in water using the surfactant system of Tween 80 and Cetomacrogol. This syrup is a solubilized oil surfactant system and is liable to heat and rate of mixing. The temperature of solution must not exceed 30˚C at the time of final mixing. The final mixing must be in continuous manner without any interruption. For the preparation of oily phase, the container must be dry.

1. Before start of batch, cool about 80.0 mL purified water and flush with nitrogen gas (purity 99.95%). Use this water for making solutions and for adjusting the volume.
2. Add 420.0 g of item 20 to the manufacturing vessel and heat to 90˚ to 95˚C.
3. Add items 2 and 3 while mixing to dissolve.
4. Add item 1 while mixing at slow speed. After addition of item 1, mix for 30 to 35 minutes at high speed, temperature 90˚ to 95˚C. Cool to 25˚ to 30˚C while mixing at low speed.
5. Bubble nitrogen gas for 10 minutes. Add item 4 to the syrup while mixing at high speed to dissolve.
6. Add item 5 to the syrup while mixing at high speed to dissolve.
7. Add 4.00 g of item 20 (25˚C) in a separate container and dissolve item 6 by using stirrer.
8. Transfer the cooled item 6 solution to the syrup tank while mixing at high speed. Mix for 15 minutes.
9. Check pH of the syrup. Limit 3.75 to 3.85. Add items 7, 8, 9, 10, and 11, one by one, to the syrup in manufacturing vessel while mixing at high speed to dissolve.
10. Mix for 10 minutes. Add 6.0 g of cold item 20 (25˚C) in a separate container and dissolve item 12.
11. Add to the manufacturing vessel while mixing at high speed. Rinse the container with cooled item 20, about 2 mL and transfer the rinsing to the syrup manufacturing vessel and mix well at high speed.
12. Add item 13 to the manufacturing vessel while mixing at high speed.

13. Warm item 14 to 70˚C in a separate stainless steel container in water bath.
14. Warm item 16 to 70˚C and mix well with item 14 under nitrogen atmosphere.
15. Add item 15 while mixing. Melt item 17 in stainless steel container and add with stirring to mix well.
16. Cool to 30˚C while mixing under nitrogen atmosphere.
17. Add items 18 and 19 to the oily-phase solution and mix for 15 minutes at high speed.
18. Check and record the volume of oily phase. Start mixing and continue mixing. Mixing must be continuous.
19. Start the addition of oily-phase solution in a thin stream. Do not stop mixing during addition of oily phase. After the addition is over, mix for a further 15 minutes at high speed.
20. Rinse the oily-phase vessel with a sufficient quantity of syrup from the syrup vessel. Transfer the rinsing to the syrup vessel.
21. Makeup the volume to 1 L with cooled item 20 (25˚C) and, finally, mix for 20 minutes at high speed.
22. Check and record the pH (limit 3.75 to 3.85 at 25˚C). Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup.

Vitamin B-Complex, A, C, D, and E Pediatric Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
8333 U	1	Vitamin A palmitate 1.7 million /gm, 50% excess	7.35
666 U	2	Vitamin D 40 million/gm	0.021
75.000	3	Polysorbate 80	75.00
0.005	4	Lemon oil terpenless	0.50
0.880	5	Vitamin E oily	0.88
0.500	6	Edatate disodium	0.50
83.33	7	Ascorbic acid, 30% excess	108.33
1.00	8	Saccharin sodium	1.00
2.500	9	Thiamine HCl, 50% excess	3.75
16.66	10	Nicotinamide, 5% excess	17.5
0.833	11	Pyridoxine HCl, 5.6% excess	0.88
2.00	12	Riboflavin sodium phosphate, 7.9% excess as riboflavin	2.16
700.00	13	Glycerin (glycerol)	700.00
250.00	14	Water, purified	250.00

MANUFACTURING DIRECTIONS

This product is a microemulsion and thermolabile preparation. The temperature of solution must not exceed 25˚C at the time of processing.

1. Load 200.0 g of item 14 to the manufacturing vessel. Bubble nitrogen gas during all stages of the process.
2. Charge items 6, 7, 8, 9, 10, 11, and 12, one by one, to the manufacturing vessel while mixing.
3. Check that all materials are dissolved completely.
4. Load item 13 to the manufacturing vessel while mixing at slow speed. Mix for 5 minutes. Add item 3 in a separate stainless steel container.
5. Mix items 1, 2, 4, and 5 one by one using stirrer. Mix for 1 hour at slow speed.
6. Add oil-phase preparation to the aqueous phase at a rate of 4 mL per minute while mixing at slow speed; keep nitrogen gas bubbling throughout the process.
7. Rinse the oil-phase container with 50.0 g of nitrogen-bubbled cooled item 14 and transfer the rinsing to the manufacturing vessel.
8. Adjust the volume to 1L using nitrogen-bubbled item 14.
9. Mix for 15 minutes at slow speed. Check and record the volume and pH (limit 2.8 to 4.2).
10. Filter the solution through prefilter and 0.2-micron membrane filter into receiving tank. Bubble with nitrogen gas for 15 minutes.

Vitamin C Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
100.0	1	Acid ascorbic white powder	100.000 g
979.00	2	Propylene glycol	979 g

MANUFACTURING DIRECTIONS

Keep under CO_2 protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only.

1. Load 868 g propylene glycol into a glass-lined or suitable stainless steel-jacketed tank.
2. While mixing, heat to 70˚ to 80˚C. Bubble CO_2 gas into the propylene glycol from the bottom of the tank.
3. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO_2 protection.
4. When the ascorbic acid is in solution, immediately cool to approximately 25˚C while continuing to mix. Also, while cooling, change CO_2 addition from tank bottom to tank top.
5. Bring to volume using propylene glycol and mix for at least 10 minutes.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L. (g)**
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor RH 40	250.00
2.00	5	Sorbic acid	2.00
628.00	6	Water	628.00

MANUFACTURING DIRECTIONS

1. Dissolve sorbic acid and benzocain in water at 60˚C.
2. Add slowly the heated mixture of Vitamin E acetate and Cremophor RH 40 (60˚ to 65˚C).
3. Cool the clear solution to about 5˚C and dissolve Lutrol F 127. A clear colorless, viscous liquid is formed.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor RH 40	250.00
2.00	5	Sorbic acid	2.00
q.s.	6	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge item 6 in suitable stainless steel-jacketed vessel, heat to 60°C.
2. Add and dissolve items 2 and 5.
3. In a separate vessel, charge items 1 and 4 (preheated to 60° to 65°C) and heat the mixture to 60° to 65°C.
4. Add step 3 to step 2 and mix until clear solution is obtained.
5. Add and dissolve item 3 and mix.

Vitamin E Capsules

Bill of Materials			
Scale (mg/capsule)	**Item**	**Material Name**	**Quantity/1000 caps (g)**
400.00	1	Vitamin E (D-alpha tocopherol 1000 units E/g)	400.00
25.00	2	Soybean oil	25.00
q.s.	3	Gelatin mass clear	q.s.

MANUFACTURING DIRECTIONS

1. Weigh and transfer into a suitable stainless steel container soybean oil and preparation of D-alpha tocopherol.
2. Mix for a minimum for 1 hour.
3. Transfer into a suitable tank through 80- to 100-mesh stainless steel screen.
4. Encapsulate 425 mg of mixture of step 3 into size 7.5 oval capsules, using gelatin mass clear.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Vitamin E acetate	50.00
160.00	2	Cremophor RH 40	160.00
q.s.	3	Preservative	q.s.
q.s.	4	Water	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Separately heat mixture of items 1 and 2 and solution of item 3 in 4 to about 65°C.
2. Add the two solutions slowly. A clear or lightly opalescent, colorless liquid should be formed.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
50.00	1	Vitamin E acetate	50.00
150.00	2	Cremophor RH 40	150.00
q.s.	3	Preservatives	q.s.
q.s.	4	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a stainless steel-jacketed vessel and heat to 65˚C.
2. In a separate vessel charge item 4 and heat to 90˚ to 95˚C and add and dissolve preservatives. Cool to 40˚C.
3. Add step 2 into step 1.
4. Fill.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/tablet)	**Item**	**Material Name**	**Quantity/L (g)**
0.10	1	Vitamin E acetate	0.100
4.50	2	Cremophor EL	4.50
570.00	3	Water	570.00
380.00	4	Ethanol	380.00

MANUFACTURING DIRECTIONS

1. Heat mixture of item 1 and 2 to about 60˚C, stir well.
2. Slowly add the warm solvent mixture of items 3 and 4. A clear, colorless liquid of low viscosity should be formed.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.10	1	Vitamin E acetate (BASF)	0.10
45.00	2	Cremophor EL	45.00
q.s.	3	Water, purified	q.s. to 1 L
380.00	4	Ethanol	380.00

MANUFACTURING DIRECTIONS

1. Charge items 1 and 2 in a suitable stainless steel-jacketed vessel, heat to 60˚C.
2. In a separate vessel (jacketed and explosion proof) charge item 3 and 4 and heat to 40˚C.
3. Add step 2 to step 1 and stir well.
4. Fill.

Xylometazoline Hydrochloride Nasal Solution

Xylometazoline hydrochloride 0.05%, Purified water, sorbitol, and mono and dibasic sodium phosphates.

Bill of Materials			
Scale (g/100 mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.100	1	Xylometazoline HCl	1.00
0.100	2	Disodium edetate (sodium EDTA)	1.00
0.700	3	Sodium chloride	7.00
0.030	4	Benzalkonium chloride (50% solution)	0.30
0.285	5	Monobasic sodium phosphate	2.85
0.306	6	Dibasic sodium phosphate	3.06
—	7	Water, purified	q.s. to 1L

MANUFACTURING DIRECTIONS

This product is a colorless membrane filtered solution; therefore, make sure that the storage tanks for solution are cleaned and free of any contamination. Use freshly boiled and cooled purified water for the manufacturing. Prepare approximately 2 L of freshly boiled and cooled purified water and store in a clean stainless steel storage vessel.

1. Add 800.0 g of item 7 (20˚ to 25˚C) to the manufacturing vessel.
2. Dissolve items 2, 3, 4, 5, and 6 one by one in step 1 while mixing for 10 minutes. Check the clarity of the solution.
3. Dissolve item 1 in 100.0 g of item 7 (25˚ to 30˚C) in a stainless steel container and add to the manufacturing vessel.
4. Rinse the drug container with 20.0 g of item 7 and add the rinsing to manufacturing vessel.
5. Make the volume up to 1 L with item 7 (20˚ to 25˚C) and finally mix for 5 minutes.
6. Check and record the pH at 25˚C (limit 6.3 ± 0.2).
7. Check the cleanliness of the storage tank. Filter the solution through a prefilter and membrane filter, 0.2 micron, into the storage tank. Recirculate first 200 to 300 mL solution.
8. Store the filtered solution in tightly closed stainless steel storage tank. Do not store more than 24 hours in stainless steel storage tank after manufacturing.

Xylometazoline Hydrochloride Children's Nasal Solution

Bill of Materials			
Scale (g/100 mL)	**Item**	**Material Name**	**Quantity/L (g)**
0.05	1	Xylometazoline hydrochloride	0.50
0.10	2	Disodium edetate (Sodium EDTA)	1.00
0.70	3	Sodium chloride	7.00
0.30	4	Benzalkonium chloride (50% solution)	0.30
0.28	5	Monobasic sodium phosphate	2.85
0.30	6	Dibasic sodium phosphate	3.06
—	7	Water, purified	q.s. to 1 L

MANUFACTURING DIRECTIONS

See above.